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(54) Title: RETINOID-GLITAZONE COMBINATIONS

(57) Abstract

Cell proliferation is inhibited by administering a combination of a retinoid and a glitazone, thereby treating disease states caused by uncontrolled cell proliferation, including cancer, restenosis, and atherosclerosis.

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RETINOID-GLITAZONE COMBINATIONS

FIELD OF THE INVENTION

This invention concerns a combination of a retinoid and a glitazone for treating diseases associated with uncontrolled cellular proliferation, such as cancer, restenosis, and atherosclerosis

BACKGROUND OF THE INVENTION

Many disease states are characterized by the uncontrolled proliferation and differentiation of cells. These disease states encompass a variety of cell types and maladies such as, cancer, atherosclerosis, and restenosis. Growth factor stimulation, autophosphorylation, and the phosphorylation of intracellular protein substrates are important biological events in the pathomechanisms of proliferative diseases.

Cell proliferation is a tightly controlled process in higher organisms. Defects in cell proliferation control can induce tumorigenesis, augment atherosclerotic lesion development, and induce restenosis following angioplasty. Cell proliferation defects may also block normal proliferative responses such as in symptomatic complications of diabetes (e.g., wound healing). Identification of genes that control the cell cycle progression has attracted a great deal of attention, since this knowledge may lead to the practical development of new therapies for cancer, cardiovascular diseases, and diabetes.

PPARγ is a nuclear hormone receptor which belongs to the peroxisome proliferator activated receptor (PPAR) family. Currently, three types of PPAR receptors have been cloned from various species and includes PPARα, PPARβ (also known as PPARδ), and PPARγ. Two PPARγ subtypes, PPARγ1 and PPARγ2, are generated from alternate splicing of the same gene. PPARγ1 and PPARγ2 share the same amino acid sequence, except that PARγ2 has 30 additional amino acids in its N terminal. Chimeric nuclear hormone receptors containing a PPAR ligand-binding domain identified the compound Wy 14643 as

a ligand for PPARα, and the thiazolidinedione, BRL 49653 (rosiglitazone), as a ligand for PPARγ (Wahli et al., *Chem. Biol.*, 1995;2:261-266). Upon ligand binding, PPAR receptors activate the transcription of many PPAR responsive genes, including acyl CoA oxidase, apolipoprotein A-I, and aP2.

Retinoids play an essential role in controlling the normal growth and differentiation of various tissues and are therefore important for prevention and treatment of premalignant and malignant lesions. It has even been found that retinoids can cause cellular repair of hyperplastic, metaplastic, and dysplastic lesions caused by carcinogens. Moreover, retinoid deficiency has been shown to enhance susceptibility to chemical carcinogenesis. Indeed, retinoids are essential for the normal cellular growth and differentiation of epithelial tissues where more than half of the total primary cancers develop in both men and women. These epithelial tissues include the mouth, bronchi, larynx, pharynx, breast, esophagus, stomach, colon, uterus, kidney, bladder, testis, prostate, pancreatic ducts, and skin. In the absence of retinoids in the diet, normal cellular growth and differentiation is disturbed.

We have now discovered that 9-cis-retinoic acid (RA) and PPARγ play important roles in the regulation of cellular growth and differentiation. In THP-1 cells, a human monocytic leukemia cell line, RA markedly induced PARγ1 RNA, whereas PPARγ2 RNA was undetected. Nuclear PPARγ1 protein content, as well as cell growth suppression, paralleled the concentration dependent RA induction of PARγ1 RNA. During a 2-day culture period, THP-1 cell number increased nearly 2-fold in the absence of RA, whereas cell number remained unchanged with 500 nM RA treatment. Addition of a glitazone PPARγ ligand, BRL 49653 significantly and concentration dependently enhanced the growth suppression ability of RA. The simultaneous treatment of THP-1 cells with a suboptimal inhibitory concentration of RA (5 nM) plus BRL 49653 (10 μM) completely arrested cell growth.

An object of this invention is thus to provide combinations of a retinoid and a glitazone and a method of treating proliferative diseases by administering a combination of a retinoid and a glitazone.

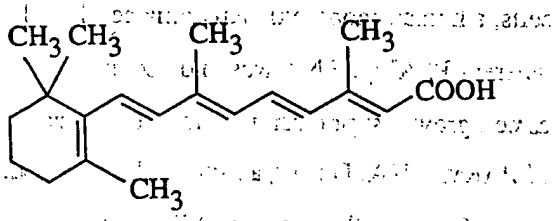
SUMMARY OF THE INVENTION

This invention provides a composition which is a combination of a retinoid and a glitazone. The invention further provides a method for inhibiting and controlling cell proliferation comprising administering an effective amount of a retinoid and an effective amount of a glitazone. The invention further provides a method for inducing cellular expression of PPARγ1 RNA and protein.

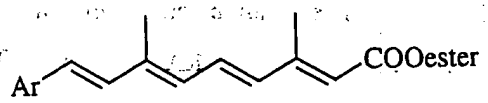
A preferred embodiment is a combination of 9-cis-RA and a glitazone selected from troglitazone, pioglitazone, and rosiglitazone.

Numerous compounds are known which are characterized as retinoids. A comprehensive discussion of retinoids is given by Dawson and Hobbs, in Chapter 2 of *The Retinoids: Biology, Chemistry, and Medicine*, 2nd ed., Sporn, Roberts, and Goodman, Raven Press, Ltd., New York, 1994. That reference is incorporated herein by reference for its teaching of the synthesis of retinoids. All that is required by this invention is that a compound characterized as a retinoid is administered to an animal in combination with a glitazone.

Preferred retinoids to be utilized in the present invention include retinoic acid of the formula

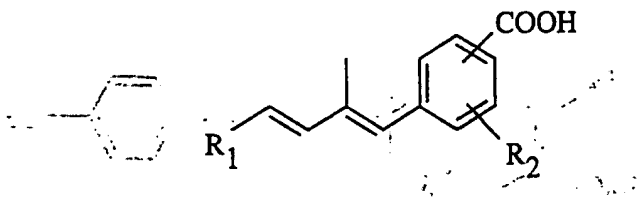


Retinoic acid derivatives also are preferred, for example, compounds of the formula



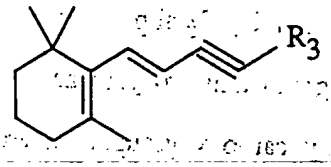
wherein Ar is an aryl group and "ester" is an organic ester forming group.

Retinoids which are dienyl benzoic acid and enzynylaryl carboxylic acids also are preferred. For example, compounds of the formula

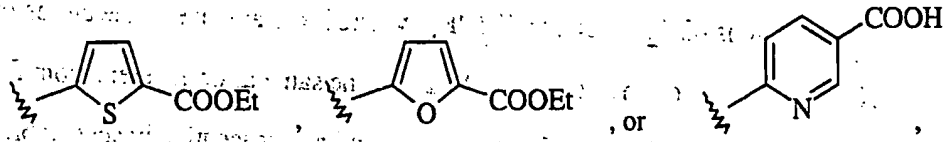


where R_1 is cycloalkyl or aryl, and R_2 is a typical phenyl substituted group such as halo, alkyl, alkoxy, alkylthio, and the like.

Compounds such as



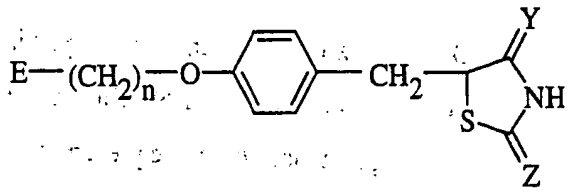
where R_3 is, for instance



also are preferred.

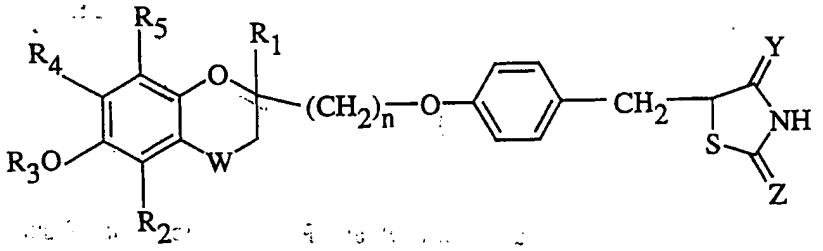
All of the retinoids required for this invention are known and available by well-known synthetic methodologies.

The glitazones are a family of antidiabetic agents characterized as being thiazolidinediones or related analogs. They are described in *Current Pharmaceutical Design*, 1996;2:85-101. Typical glitazones have the formula



where n is 1, 2, or 3, Y and Z independently are O or NH; and E is a cyclic or bicyclic aromatic or non-aromatic ring, optionally containing a heteroatom selected from oxygen or nitrogen.

Preferred glitazones have the formula



wherein:

R_1 and R_2 independently are hydrogen or C_1-C_5 alkyl;

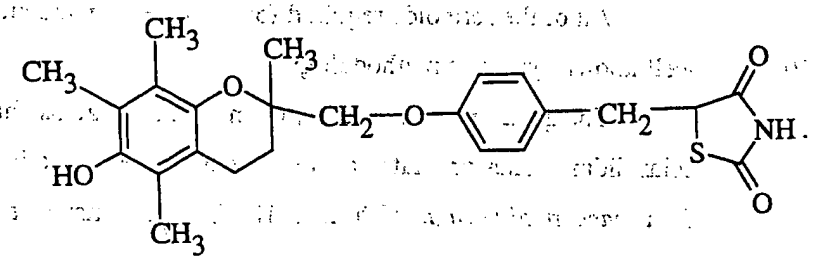
R_3 is hydrogen, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_6 alkoxy) carbonyl group, or an aralkyloxycarbonyl group;

R_4 and R_5 independently are hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or R_4 and R_5 together are C_1-C_4 alkylenedioxy;

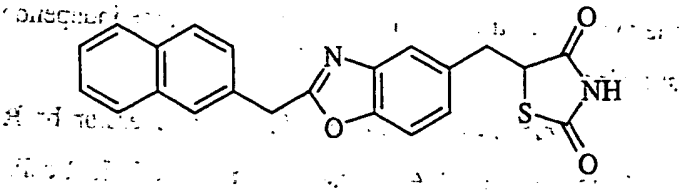
W is $-CH_2-$, >CO, or $CHOR_6$, where R_6 is any one of the atoms or groups defined for R_3 and may be the same as or different from R_3;

n, Y, and Z are as defined above, and pharmaceutically acceptable salts thereof.

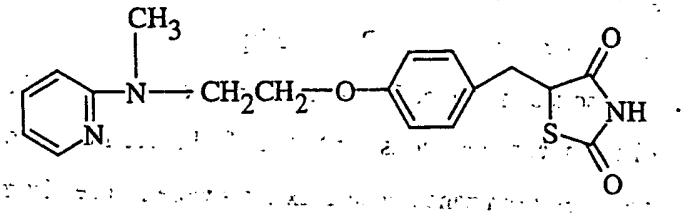
An especially preferred glitazone is troglitazone having the formula



Other glitazones that can be employed in this invention are described in United States Patent No. 5,457,109, which is incorporated herein by reference. Other specific glitazones which are preferred include ciglitazone, pioglitazone, englitazone, TA 174, which has the formula



and BRL 49653, which is now called rosiglitazone and has the formula



Additionally preferred glitazones include:

5-(4-[2-[1-(4-2′-Pyridylphenyl)ethylideneaminooxy]ethoxy]benzyl]-thiazolidine-2,4-dione;

5-(4-[5-Methoxy-3-methylimidazo[5,4-b]pyridin-2-yl-methoxy)benzyl]-thiazolidine-2,4-dione, or its hydrochloride;

5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)benzyl]-thiazolidine-2,4-dione;

5-[4-(1-Methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione; and

5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione.

Another embodiment of the invention is a method for inhibiting cell proliferation comprising administering a glitazone together with a retinoid. A preferred method comprises treating cancer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. RA induced growth suppression in THP-1 cells. THP-1 cells were plated out at around 150000 cells/mL and cultured for up to 2 days in the presence of RA at different concentrations. Cell number was counted daily, and

the average of the experimental data from three independent experiments were showing.

Figure 2. Induction of PPARγ1 expression by RA in THP-1 cells. (*A*) Total cellular RNA was isolated from the THP-1 cells treated with either DMSO or 500 nM RA for 1 day. RNase protection assay was performed as described under "Experimental Procedures." RNA was hybridized to both PPARγ probe and GAPDH probe. The PPARγ probe recognizes both PPARγ1 RNA (94 bp signals) and PPARγ2 (163 bp signals). (*B*) Top panel, total cellular RNA was isolated from the THP-1 cells treated with either DMSO or 500 nM RA at different concentrations (5 nM to 500 nM) for 1 day and hybridized to PPARγ probe. Bottom panel, nuclear extracts were isolated from the THP-1 cells treated with either DMSO or RA at different concentrations (0.05 nM to 500 nM) for 1 day and assayed for PPARγ1 protein by western blot analysis. The strong band above the PPARγ1 band is nonspecific.

Figure 3. The simultaneous treatment of the THP-1 cells with RA and BRL 49653 resulted in an additive effect on the growth suppression. THP-1 cells were plated out at around 150000 cells/mL and cultured for up to 2 days in the presence of different stimulators. Cell number was counted daily. (*A*) The THP-1 cells were cultured with either DMSO or BRL 49653 at the indicated concentrations. (*B*) The THP-1 cells were cultured with either DMSO or the combination of RA and BRL 49653 at the indicated concentrations. (*C*) THP-1 cells were harvested after treated with RA, or BRL 49653, or the combination of RA and BRL 49653 for 1 day. The cell cycle flow cytometry analysis was then carried out as described under "Experimental Procedures." The results showing were the average of the experimental data from three independent experiments.

Figure 4. The RA-induced growth suspension did not result in the differentiation of the THP-1 monocytes into macrophages. (*A*) Florescence activated cell sorting (FACS) histogram of CD14 and CD15 cell surface antigens of the THP-1 cells. THP-1 cells were treated with RA or DMSO for 1 day and harvested for the immunocytometry analysis as described under "Experimental Procedures." (*B*) The cell numbers of the suspended THP-1 cells were counted after treated with DMSO, RA, PMA, or RA plus PMA for 1 day and expressed as

the percent of the initial cell number when THP-1 cells were plated out for different treatments. The results showing were the average of the experimental data from three independent experiments.

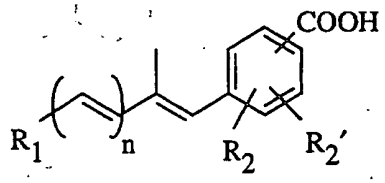
Figure 5: The induction of PPARγ expression by RA was specific to undifferentiated THP-1 monocytes. (*A*) Total cellular RNA was isolated from the THP-1 cells treated with the indicated stimulators for 1 day. RNase protection assay was performed as described under "Experimental Procedures." RNA was hybridized to both PPARγ probe and GAPDH probe. (*B*) THP-1 cells were first differentiated with 2×10^{-7} M PMA for 1 day, and then treated with either DMSO or 500 nM 9-cis-RA for another day. Total cellular RNA was isolated afterward and used for the RNase protection assay with both PPARγ probe and GAPDH probe.

DETAILED DESCRIPTION OF THE INVENTION

All that is required for this invention is to administer an effective amount of a retinoid to an animal in combination with an effective amount of a glitazone, said amounts being effective for reducing cell proliferation, and/or inducing cellular expression of PPARγ1.

Preferred retinoids to be utilized are benzoic acids and carboxylic acids and esters thereof, particularly C_1-C_6 alkyl esters, such as methyl, ethyl, isopropyl, isopentyl, and n-hexyl.

Typical benzoic acids to be utilized include those of the formula

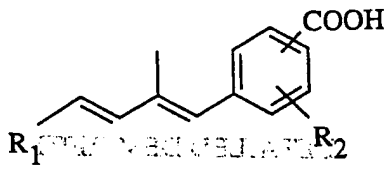


wherein R_1 is cycloalkyl or aryl and R_2' independently are:

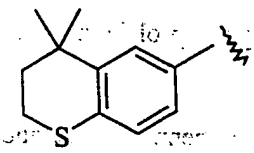
R_2 substituent group such as halo, hydroxy, amine, mono- and dialkyl amino, C_1-C_6 alkyl, C_1-C_6 alkoxy, or C_1-C_6 alkylthio, and n is 0 or 1. The cycloalkyl group can be a single ring, for instance a C_3-C_7 cycloalkyl ring, optionally

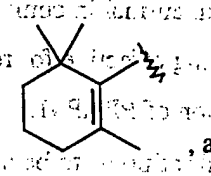
substituted with halo, alkyl, alkoxy, alkylthio, or the like, or bicyclic. Similarly, the aryl can be monocyclic or bicyclic, for instance, phenyl or naphthyl, it can be cycloalkyl fused to an aromatic ring, for instance, a benzocyclohexane or benzocycloheptane, and any of the ring systems can contain heteroatoms, for instance, 1, 2, or 3 heteroatoms selected from sulfur, oxygen, and nitrogen. The rings can also be substituted, for example, with 1, 2, or 3 groups such as R_2 and R_2'. Many of the retinoids have an alkylene chain which can exist as cis and trans isomers. Both the all cis and all trans, as well as mixtures, can be used herein.

Examples of preferred retinoids to be utilized in the method of this invention include those having the following structures:

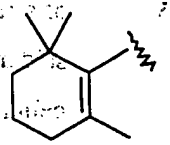


where R_1 is, for instance

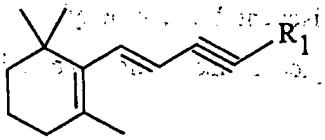




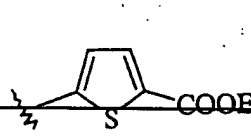
, and

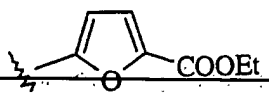


and R_2 is hydrogen, halo, or alkoxy;

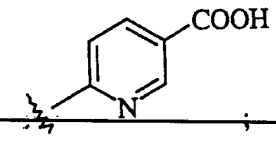


where R_1 is





, or



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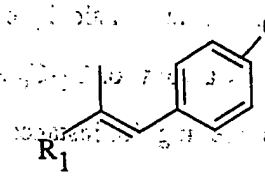
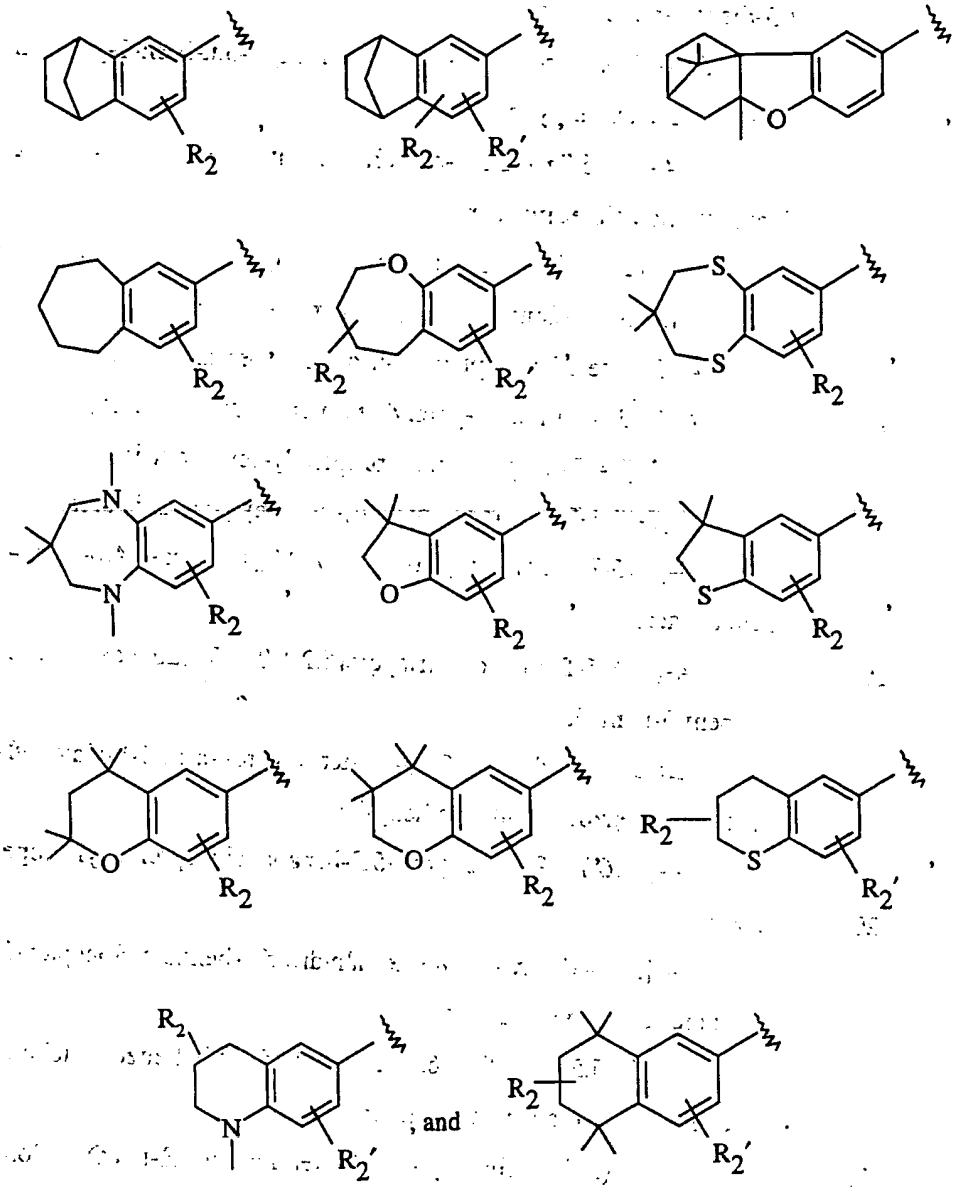


where R_1 is alkyl or dialkylphenyl, or a bi- or tricyclic ring such as:



The typical specific retinoids which can be utilized in the method of the invention include the following:

4-[4-(4,4-Dimethyl-thiochroman-6-yl)-2-methyl-buta-1,3-dienyl]-benzoic acid;

3-Fluoro-4-[2-methyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-buta-1,3-dienyl]-benzoic acid;

3-Methoxy-4-[2-methyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-buta-1,3-dienyl]-benzoic acid;

5-[4-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-3-en-1-ynyl]-thiophene-2-carboxylic acid ethyl ester;

5-[4-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-3-en-1-ynyl]-furan-2-carboxylic acid ethyl ester;

6-[4-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-3-en-1-ynyl]-nicotinic acid;

4-[2-(3-tert-Butyl-phenyl)-propenyl]-benzoic acid;

4-[2-(4-tert-Butyl-phenyl)-propenyl]-benzoic acid;

4-[2-(3,4-Dimethyl-phenyl)-propenyl]-benzoic acid;

4-[2-(3,4-Diethyl-phenyl)-propenyl]-benzoic acid;

4-[2-(3,4-Diisopropyl-phenyl)-propenyl]-benzoic acid;

4-[2-(5-Isobutyl-tricyclo[6.2.1.0>2,7_]undeca-2,4,6-trien-4-yl)-propenyl]-benzoic acid;

4-[2-(3,6-Dimethoxy-tricyclo[6.2.1.0>2,7_]undeca-2,4,6-trien-4-yl)-propenyl]-benzoic acid;

Benzoic acid, 4-[2-(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)ethenyl]-;

4-[2-(6,7,8,9-Tetrahydro-5H-benzocyclohepten-2-yl)propenyl]-benzoic acid;

4-[2-(7-Methyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(5,5-Dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(3,7,7-Trimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid methyl ester;

4-[2-(7,7-Dimethyl-3-octyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid;

4-[2-(7-Ethyl-7-methyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

Benzoic acid, 4-[2-(5,6,8,9-tetrahydro-spiro[7H-benzocycloheptene-7,1'-cyclopropane]-2-yl)-1-propenyl]-, ethyl ester;

Benzoic acid, 4-[2-(5,6,8,9-tetrahydro-spiro[7H-benzocycloheptene-7,1'-cyclopentane]-2-yl)-1-propenyl]-, ethyl ester;

4-[2-(7-Oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(9-Methyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(5,5,9-Trimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(7,7,9-Trimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(5,9,9-Trimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(7,7,9,9-Tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid;

4-[2-(6,6,8,8-Tetramethyl-7-oxo-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yl)-propenyl]-benzoic acid ethyl ester;

4-[2-(4,4-Dimethyl-chroman-7-yl)-propenyl]-benzoic acid;

4-[2-(4,4-Dimethyl-1,1-dioxo-thiochroman-7-yl)-propenyl]-benzoic acid;

4-[2-(1,4,4-Trimethyl-1,2,3,4-tetrahydro-quinolin-7-yl)-propenyl]-benzoic acid;

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-propenyl]-benzoic acid;

4-[2-(2,3-Dihydro-benzo[1,4]dithiin-6-yl)-propenyl]-benzoic acid;

4-[2-(1,4-Dimethyl-1,2,3,4-tetrahydro-quinoxalin-6-yl)-propenyl]-benzoic acid;

4-[2-(2,3,4,5-Tetrahydro-benzo[b]oxepin-8-yl)-propenyl]-benzoic acid;

4-[2-(2,3,4,5-Tetrahydro-benzo[b]oxepin-7-yl)-propenyl]-benzoic acid;

4-[2-(2,3,4,5-Tetrahydro-benzo[b]thiepin-8-yl)-propenyl]-benzoic acid;

4-[2-(5-Methyl-2,3,4,5-tetrahydro-benzo[b]thiepin-8-yl)-propenyl]-benzoic acid;

4-[2-(5,5-Dimethyl-2,3,4,5-tetrahydro-benzo[b]thiepin-8-yl)-propenyl]-benzoic acid;

4-[2-(3,3-Dimethyl-2,3,4,5-tetrahydro-benzo[b]thiepin-8-yl)-propenyl]-benzoic acid;

4-[2-(2,3,4,5-Tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(5-Methyl-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3-Methyl-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3,5,5-Trimethyl-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3,3-Dimethyl-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(1,1-Dioxo-2,3,4,5-tetrahydro-benzo[b]thiepin-8-yl)-propenyl]-benzoic acid;

4-[2-(1,1-Dioxo-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(5,5-Dimethyl-1,1-dioxo-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3-Methyl-1,1-dioxo-2,3,4,5-tetrahydro-benzo[b]thiepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-propenyl]-benzoic acid;

4-[2-(3-Methyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-propenyl]-benzoic acid;

4-[2-(7,7-Dimethyl-7,8-dihydro-6H-5-oxa-9-thia-benzocyclohepten-2-yl)-propenyl]-benzoic acid;

4-[2-(7,8-Dihydro-6H-5,9-dithia-benzocyclohepten-2-yl)-propenyl]-benzoic acid;

4-[2-(7-Methyl-7,8-dihydro-6H-5,9-dithia-benzocyclohepten-2-yl)-propenyl]-benzoic acid;

4-[2-(5-Methyl-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepin-8-yl)-propenyl]-benzoic acid;

4-[2-(3,5-Dimethyl-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepin-8-yl)-propenyl]-benzoic acid;

4-[2-(2,2-Dimethyl-benzo[1,3]dioxol-5-yl)-propenyl]-benzoic acid;

4-[2-(2,2-Dimethyl-benzo[1,3]dithiol-5-yl)-propenyl]-benzoic acid;

4-Styryl-benzoic acid;

4-[2-(4-tert-Butyl-phenyl)-vinyl]-benzoic acid;

4-(2-Tricyclo[6.2.1.0>2,7_]undeca-2,4,6-trien-4-yl-vinyl)-benzoic acid;

Benzoic acid, 4-[2-(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)ethenyl]-;

4-[2-(4-Methoxy-2,3,6-trimethyl-phenyl)-vinyl]-benzoic acid;

4-{2-[4-(3-Methyl-but-2-enyloxy)-phenyl]-vinyl}-benzoic acid ethyl ester;

4-{2-[2-Methyl-4-(3-methyl-but-2-enyloxy)-phenyl]-vinyl}-benzoic acid ethyl ester;

4-{2-[2-Methyl-4-(3-methyl-but-2-enylsulfanyl)-phenyl]-vinyl}-benzoic acid ethyl ester;

4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Methoxy-4,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Methoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1,4-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Ethoxy-3-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Isopropoxy-3-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(3-Methoxy-5,5,8,8-tetramethyl-1-propoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Butoxy-3-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-[2-(1-Hexyloxy-3-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid;

4-(1,1,3,3-Tetramethyl-indan-5-ylethynyl)-benzoic acid;

4-(1,1,2,3,3-Pentamethyl-indan-5-ylethynyl)-benzoic acid;

4-(3,8,8-Trimethyl-5,6,7,8-tetrahydro-naphthalen-2-ylethynyl)-benzoic acid;

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylethynyl)-benzoic acid;

6-(4,4,7-Trimethyl-chroman-6-ylethynyl)-nicotinic acid ethyl ester;

6-(3,3,4,4-Tetramethyl-chroman-6-ylethynyl)-nicotinic acid ethyl ester;

6-(3,3,4,4,7-Pentamethyl-chroman-6-ylethynyl)-nicotinic acid ethyl ester;

6-(4,4-Dimethyl-thiochroman-6-ylethynyl)-nicotinic acid ethyl ester;

6-(4,4,7-Trimethyl-thiochroman-6-ylethynyl)-nicotinic acid ethyl ester;

4-[5-(1,1,2,3,3-Pentamethyl-indan-5-yl)-1H-pyrazol-3-yl]-benzoic acid methyl ester;

4-[5-(3-Methyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1H-pyrazol-3-yl]-benzoic acid methyl ester;

4-[3-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-pyrazol-1-yl]-benzoic acid;

4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1H-imidazol-4-yl]-benzoic acid ethyl ester;

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-1H-imidazol-2-yl]-benzoic acid methyl ester;

4-[5-Oxo-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-4,5-dihydro-pyrazol-1-yl]-benzoic acid;

4-[2-Mercapto-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-imidazol-1-yl]-benzoic acid;

4-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxazol-2-yl]-benzoic acid methyl ester;

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxazol-2-yl]-benzoic acid methyl ester;

4-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxazolidin-3-yl]-benzoic acid ethyl ester;

4-[3-(7-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-isoxazol-5-yl]-benzoic acid;

4-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-thiazol-2-yl]-benzoic acid methyl ester;

6-(3-Adamantan-1-yl-4-hexyloxy-phenyl)-naphthalene-2-carboxylic acid;

6-(3-Adamantan-1-yl-4-decyloxy-phenyl)-naphthalene-2-carboxylic acid;

2-Naphthalenecarboxylic acid, 6-(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)-;

6-[4-(Methoxy-3-(1-methyl-1-nonyloxy-ethyl)-phenyl]-naphthalene-2-carboxylic acid;

6-(3,4-Dimethoxy-phenyl)-naphthalene-2-carboxylic acid;

6-[4-(Adamantan-1-ylsulfanyl)-phenyl]-naphthalene-2-carboxylic acid;

8-Methoxy-5',5',8',8'-tetramethyl-5',6',7',8'-tetrahydro-[2,2']binaphthalenyl-6-carboxylic acid;

6-(3-Adamantan-1-yl-4-methoxy-phenyl)-4-hydroxy-1-methyl-naphthalene-2-carboxylic acid;

2-(4-tert-Butyl-phenyl)-benzofuran-6-carboxylic acid;

2-(4-tert-Butyl-phenyl)-benzo[b]thiophene-6-carboxylic acid;

2-(4-tert-Butyl-phenyl)-1H-indole-6-carboxylic acid;

2-(3-tert-Butyl-4-methoxy-phenyl)-benzofuran-6-carboxylic acid;

2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzofuran-6-carboxylic acid;

2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzooxazole-6-carboxylic acid;

2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-3H-benzoimidazole-5-carboxylic acid;

2-(3-Adamantan-1-yl-4-methoxy-phenyl)-benzofuran-6-carboxylic acid;

2-(3-Adamantan-1-yl-4-methoxy-phenyl)-benzo[b]thiophene-6-carboxylic acid;

2-(3-Adamantan-1-yl-4-methoxy-phenyl)-3H-benzoimidazole-5-carboxylic acid;

2-(3-Adamantan-1-yl-4-hydroxy-phenyl)-3H-benzoimidazole-5-carboxylic acid;

2-(3-Adamantan-1-yl-4-decyloxy-phenyl)-benzooxazole-6-carboxylic acid;

Benzo[b]thiophene-6-carboxylic acid, 2-(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)-;

6-[Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methyl]-naphthalene-2-carboxyl ic acid;

6-[Acetoxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methyl]-naphthalene-2-carboxyl ic acid;

6-(1,1,3,3-Tetramethyl-indane-5-carbonyl)-naphthalene-2-carboxylic acid;

6-[Hydroxy-(1,1,2,3,3-pentamethyl-indan-5-yl)-methyl]-naphthalene-2-carboxylic acid;

6-(6,7-Dimethyl-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid;

6-(6-Methoxy-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid;

6-(6-Methoxy-5,8-dimethyl-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid;

6-[Hydroxy-(6-methoxy-5,8-dimethyl-naphthalen-2-yl)-methyl]-naphthalene-2-carboxylic acid;

6-(6-Methoxy-5,8-dimethyl-naphthalen-2-ylmethyl)-naphthalene-2-carboxylic acid;

6-(4,4-Dimethyl-chroman-6-carbonyl)-naphthalene-2-carboxylic acid;

6-[(4,4-Dimethyl-chroman-6-yl)-hydroxy-methyl]-naphthalene-2-carboxylic acid;

6-(4,4-Dimethyl-chroman-6-ylmethyl)-naphthalene-2-carboxylic acid;

2-Naphthalenecarboxylic acid, 6-[(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)carbonyl]-;

6-(2,2-Dimethyl-chroman-6-carbonyl)-naphthalene-2-carboxylic acid;

6-(4-tert-Butyl-benzoyl)-naphthalene-2-carboxylic acid;

6-[(2,4-Di-tert-butyl-phenyl)-hydroxy-methyl]-naphthalene-2-carboxylic acid;

6-(2,4-Diisopropyl-benzoyl)-naphthalene-2-carboxylic acid;

6-(2,4-Diisopropyl-benzyl)-naphthalene-2-carboxylic acid;

6-(4-Cyclohexyl-benzoyl)-naphthalene-2-carboxylic acid;

6-(4-Phenoxy-benzoyl)-naphthalene-2-carboxylic acid;

6-(4-Methoxy-benzoyl)-naphthalene-2-carboxylic acid;

6-(6-Methoxy-biphenyl-3-carbonyl)-naphthalene-2-carboxylic acid;

6-(3-Adamantan-1-yl-4-methoxy-benzoyl)-naphthalene-2-carboxylic acid;

6-(4-Methoxy-2,3,6-trimethyl-benzoyl)-naphthalene-2-carboxylic acid;

2-(1,1,3,3-Tetramethyl-indane-5-carbonyl)-benzoic acid;

2-(1,1,2,3,3-Pentamethyl-indane-5-carbonyl)-benzoic acid;

2-(3,6-Dimethoxy-tricyclo[6.2.1.0>2,7_]undeca-2(7),3,5-triene-4-carbonyl)-benzoic acid;

2-(1,1,2,3,3-Pentamethyl-indane-5-carbonyl)-cyclohex-1-enecarboxylic acid;

2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-cyclohexanecarboxylic acid;

2-(1,1,2,3,3-Pentamethyl-indane-5-carbonyl)-cyclohexanecarboxylic acid;

4-(Tricyclo[6.2.1.0>2,7_]undeca-2(7),3,5-triene-4-carbonyl)-benzoic acid;

4-(1,1,2,3,3-Pentamethyl-indane-5-carbonyl)-benzoic acid;

4-[Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methyl]-benzoic acid;

4-(2,4-Diisopropyl-benzoyl)-benzoic acid;

4-[(2,4-Diisopropyl-phenyl)-hydroxy-methyl]-benzoic acid;

4-(3,5-Di-tert-butyl-4-hydroxy-benzoyl)-benzoic acid;

4-[Hydroxy-(6-methoxy-5,8-dimethyl-naphthalen-2-yl)-methyl]-benzoic acid;

4-[(4,4-dimethyl-thiochroman-6-yl)-hydroxy-methyl]-benzoic acid;

4-(3-Oxo-3-phenyl-propenyl)-benzoic acid;

4-[3-(3,4-Diethyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(3,4-Diisopropyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(4-tert-Butyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(3-tert-Butyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(3,5-Di-tert-butyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(2,5-Di-tert-butyl-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-Oxo-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-benzoic acid;

4-[3-Oxo-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-benzoic acid;

2-Hydroxy-4-[3-oxo-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-benzoic acid;

4-[3-(4,4-Dimethyl-chroman-6-yl)-3-oxo-propenyl]-benzoic acid;

4-[3-(4,4-Dimethyl-chroman-7-yl)-3-oxo-propenyl]-benzoic acid;

4-[3-(4,4-Dimethyl-thiochroman-6-yl)-3-oxo-propenyl]-benzoic acid;

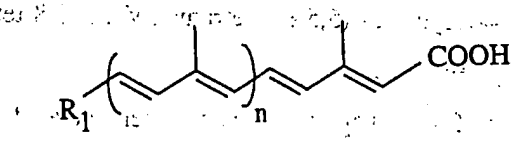
4-[3-(3,4-Dimethoxy-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[1-Hydroxy-3-(2-hydroxy-phenyl)-3-oxo-propenyl]-benzoic acid;

4-[3-(5-tert-Butyl-2-hydroxy-phenyl)-1-hydroxy-3-oxo-propenyl]-benzoic acid; and

4-[3-(4-tert-butyl-2-hydroxy-phenyl)-1-hydroxy-3-oxo-propenyl]-benzoic acid.

Other retinoids which can be utilized to lower plasma levels of Lp(a) include polyolefinic carboxylic acids, aldehydes, and alcohols having the general formula



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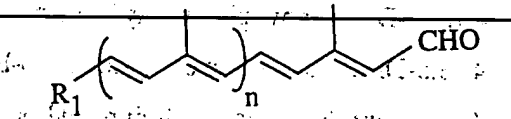

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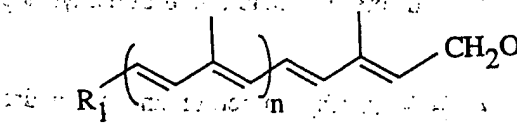
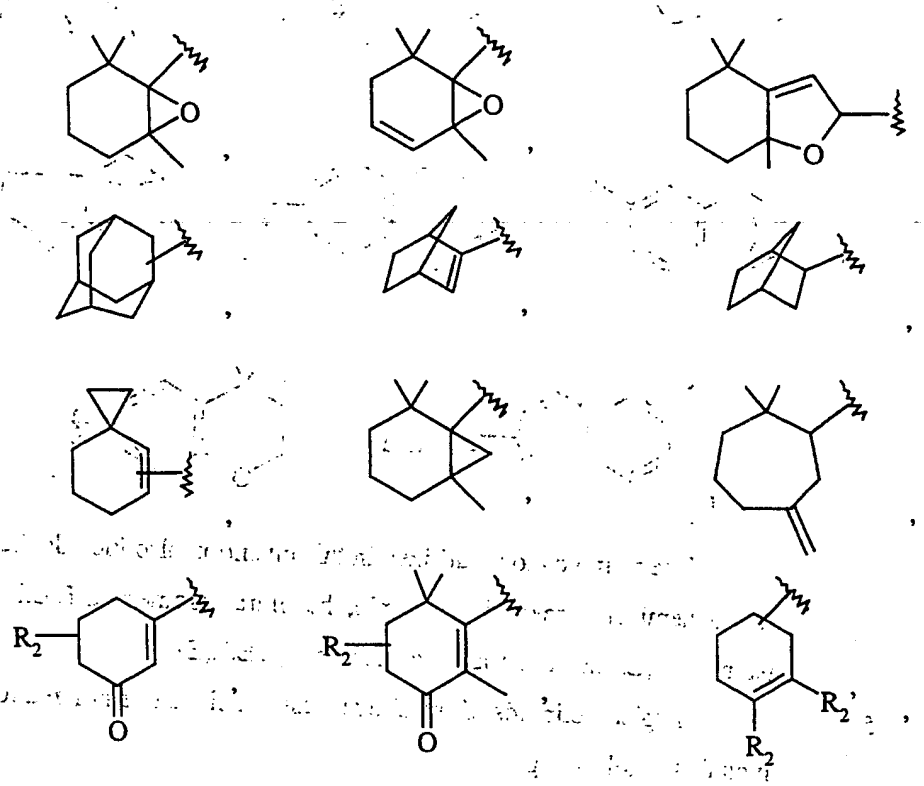
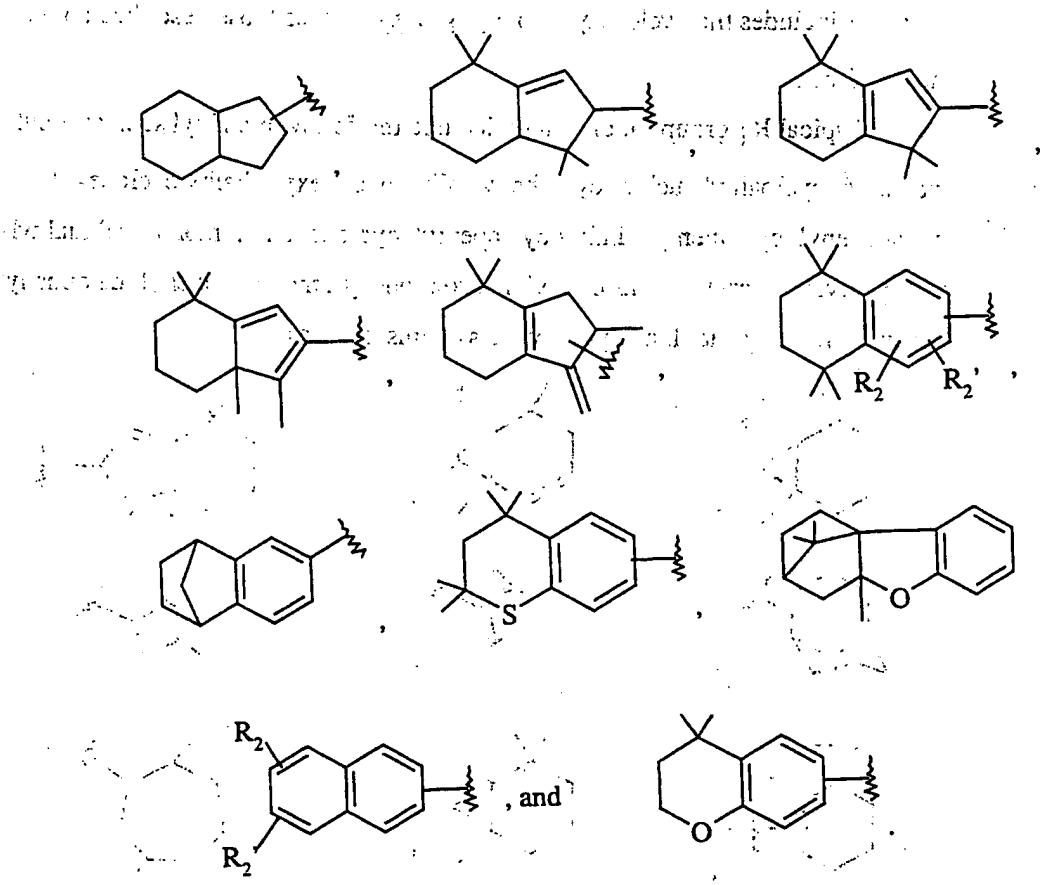


where R_1 includes the cycloalkyl and aryl groups such as those described above, and n is 0 or 1.

Typical R_1 groups additionally include the following: alkyl such as ethyl and hexyl; cycloalkyl such as cyclohexyl, alkylcyclohexyl, dialkylcyclohexyl, cyclohexenyl, cyclopentyl, dialkylcyclopentyl, cyclopentenyl, mono- and dialkyl-cyclopentyl; and aryl such as phenyl, hydroxyphenyl, methoxyphenyl, halophenyl, thienyl, furanyl, pyridyl, and polycyclic systems, such as





, and

The retinoids to be utilized in this invention also include the various stereochemical isomers, for example, the all transisomers (E,E,E,E), the 9-cis isomers (E,E,Z,E), and the 13-cis isomers (Z,E,E,E).

Typical retinoids of the above class which can be utilized to lower Lp(a) include the following:

3,7-Dimethyl-undeca-2,4,6,8-tetraenal;

9-Cyclohexyl-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,2,6-trimethyl-cyclohexyl)-nona-2,4,6,8-tetraenal;

9-Cyclohex-1-enyl-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2-methyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

9-(6,6-Dimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

9-(2,6-Dimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3-Methyl-9-(2,5,5-trimethyl-cyclopent-1-enyl)-nona-2,4,6,8-tetraenal;

10-Isopropyl-3-methyl-dodeca-2,4,6,8,10-pentaenal;

3-Methyl-dodeca-2,4,6,8,10-pentaenal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohexa-1,3-dienyl)-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-phenyl-nona-2,4,6,8-tetraenal;

9-(3-Hydroxy-2,6,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,6,6-trimethyl-3-oxo-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,2,6-trimethyl-7-oxa-bicyclo[4.1.0]hept-1-yl)-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,2,6-trimethyl-7-oxa-bicyclo[4.1.0]hept-4-en-1-yl)-nona-2,4,6,8-tetraenal;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3-Methyl-9-(2,4,5-trimethyl-thiophen-3-yl)-nona-2,4,6,8-tetraenal;

3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enzyl)-nona-2,4,6,7-tetraen-1-ol;

All trans-9-(4-Dimethylamino-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

3,7,11-Trimethyl-dodeca-2,4,6,8,10-pentaenal;

3,7-Dimethyl-9-(2,2,6-trimethyl-cyclohexylidene)-nona-2,4,6,8-tetraenal;

3-Methyl-7-(4,4,7a-trimethyl-2,4,5,6,7,7a-hexahydro-benzofuran-3-yl)-octa-2,4,6-trienal;

9-(2,2-Dimethyl-6-methylene-cyclohexyl)-3,7-dimethyl-nona-2,4,6,8-tetraenal;

9-Adamantan-2-ylidene-3,7-dimethyl-nona-2,4,6,8-tetraenal;

5,9-Dimethyl-11-(2,6,6-trimethyl-cyclohex-1-enyl)-undeca-2,4,6,8,10-pentaenal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,8-dienal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6-trienal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,6,8-trien-1-ol;

2,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

13-(2,6,6-Trimethyl-cyclohex-1-enyl)-trideca-2,4,6,8,10,12-hexaenal;

17-(2,6,6-Trimethyl-cyclohex-1-enyl)-heptadeca-2,4,6,8,10,12,14,16-octaenal;

7-Ethyl-3-methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

2,3,7-Trimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

7-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

2,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraen-1-ol;

(E,E,E)-3,7-dimethyl-undeca-2,6,8-trien-4-yn-1-ol;

(Z,E,E)-3,7-dimethyl-undeca-2,6,8-trien-4-yn-1-ol;

(E,E,E)-2,2,7-trimethyl-3-methylene-undeca-4,6,8-trienoic acid;

(Z,E,E,E)-2,3,7-trimethyl-undeca-2,4,6,8-tetraenoic acid;

7-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

{5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclohept-3-enylidene}-acetaldehyde;

{4-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclohept-2-enylidene}-acetaldehyde;

3-Bromo-7-methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

6-Fluoro-7-methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

7-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-4,6,8-trien-2-ynal;

6,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

3-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

9-(2,6,6-Trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

7-Methyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

{5-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclohept-3-enylidene}-acetaldehyde;

{4-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclohept-2-enylidene}-acetaldehyde;

4,8-Dimethyl-10-(2,6,6-trimethyl-cyclohex-1-enyl)-deca-3,5,7,9-tetraen-2-one;

2-Bromo-3,7-dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

2-Fluoro-3,7-dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenal;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid;

3-Methyl-6-(1,1,4,4-tetramethyl-1,4,5,6,7,7a-hexahydro-inden-2-ylidene)-hexa-2,4-dienoic acid;

3-Methyl-6-(1,1,4,4-tetramethyl-1,4,5,6,7,7a-hexahydro-inden-2-ylidene)-hexa-2,4-dienoic acid;

(E,Z,E,E)-3-tert.-butyl-7-methyl-undec-2,4,6,8-tetraen-1-ol;

3-Methyl-6-(1,1,4,4-tetramethyl-4,5,6,7-tetrahydro-1H-inden-2-yl)-hexa-3,5-dienoic acid;

3-Methyl-6-(1,1,4,4-tetramethyl-4,5,6,7-tetrahydro-1H-inden-2-yl)-hexa-3,5-dienoic acid;

3-Methyl-6-(3,3a,7,7-tetramethyl-4,5,6,7-tetrahydro-3aH-inden-2-yl)-hexa-3,5-dienoic acid;

3-Methyl-6-(3,3a,7,7-tetramethyl-4,5,6,7-tetrahydro-3aH-inden-2-yl)-hexa-3,5-dienoic acid;

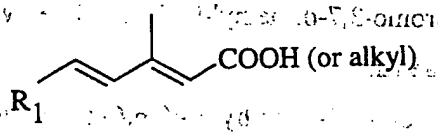
3-Methyl-6-(2,4,4-trimethyl-1-methylene-2,3,4,5,6,7-hexahydro-1H-inden-2-yl)-hexa-2,4-dienoic acid;

2,3,7-trimethyl-9-(2,6,6-trimethyl-cyclohexa-1,3-dienyl)-nona-2,4,6,8-tetraenoic acid;

9-(4-dimethylaminophenyl)-2,3,7-trimethyl-nona-2,4,6,8-tetraenoic acid; and

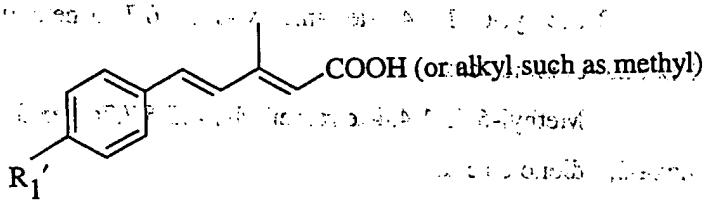
3-Methyl-6-(2,4,4-trimethyl-1-methylene-2,3,4,5,6,7-hexahydro-1H-inden-2-yl)-hexa-2,4-dienoic acid.

Additional retinoids which can be utilized are aryldienoic acids of the general formula

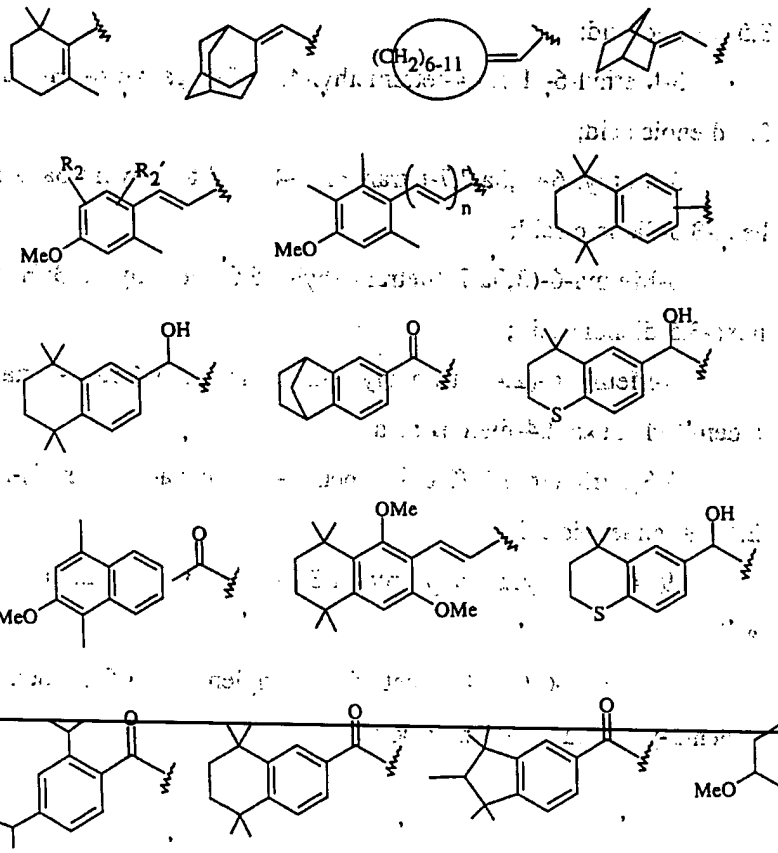


where R_1 is aryl, especially phenyl substituted with further aryl, cycloalkyl, and fused cycloalkylaryl groups.

Preferred retinoids have the formula



where R_1' is aryl, cycloalkyl, or polycyclo of the following general formulas:



Specific retinoids included within the above general formulas include the following:

5-(4-Cycloundecylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoic acid;

5-(4-Bicyclo[2.2.1]hept-2-ylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoic acid;

5-{4-[2-(4-Methoxy-2,3,6-trimethyl-phenyl)-vinyl]-phenyl}-3-methyl-penta-2,4-dienoic acid;

2,4-Pentadienoic acid, 3-methyl-5-(2,3,4,4a-tetrahydro-4a,10,10-trimethyl-1H-3,9b-methanodibenzofuran-8-yl)-;

3-{4-[2-(4-Methoxy-2,3,6-trimethyl-phenyl)-vinyl]-phenyl}-acrylic acid;

3-{4-[4-(4-Methoxy-2,3,6-trimethyl-phenyl)-2-methyl-buta-1,3-dienyl]-phenyl}-acrylic acid;

3-{4-[2-(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenyl}-acrylic acid;

3-{4-[Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methyl]-phenyl}-acrylic acid;

3-{4-[(4,4-Dimethyl-thiochroman-6-yl)-hydroxy-methyl]-phenyl}-2-methyl-acrylic acid;

3-[4-(1,2,3,4-Tetrahydro-1,4-methano-naphthalene-6-carbonyl)-phenyl]-acrylic acid;

3-[4-(2,4-Diisopropyl-benzoyl)-phenyl]-2-methyl-acrylic acid;

3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-phenyl]-acrylic acid;

2-Methyl-3-[4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-phenyl]-acrylic acid;

2-Methyl-3-[4-(1,1,2,3,3-pentamethyl-indane-5-carbonyl-carbonyl)-phenyl]-acrylic acid;

3-[4-(4-Methoxy-2,5-dimethyl-benzoyl)-phenyl]-2-methyl-acrylic acid;

{2-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-cycloheptylidene}-acetaldehyde;

2-Methyl-3-[3-methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-cyclopent-1-enecarbaldehyde;

3-Methyl-4-{3-[2-(2,6,6-trimethyl-cyclohex-1-enyl)-vinyl]-cyclohex-2-enylidene}-but-2-enal;

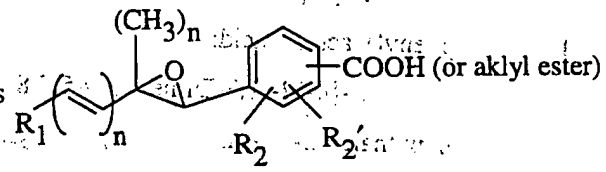
{2-[3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienylidene]-cyclohexylidene}-acetaldehyde;

{3-[2-Methyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-buta-1,3-dienyl]-cyclohex-2-enylidene}-acetaldehyde;

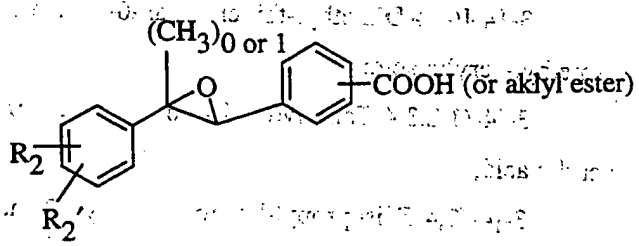
{4-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclohept-2-enylidene}-acetaldehyde; and

{4-[1-Methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allylidene]-cyclopent-2-enylidene}-acetaldehyde.

Still other compounds which are included within the general class of retinoids are retinoidal oxiranes, such as



with preferred oximes having the formula:



Typical retinoidal oxiranes include

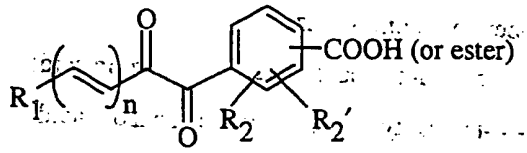
4-[3-(4-tert-Butyl-phenyl)-oxiranyl]-benzoic acid;

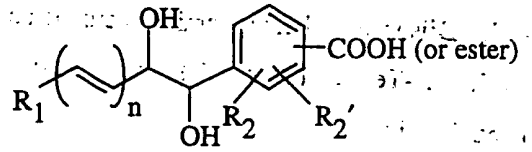
4-[3-(3-tert-Butyl-phenyl)-oxiranyl]-benzoic acid;

4-[3-(3,4-Diethyl-phenyl)-3-methyl-oxiranyl]-benzoic acid; and

4-[3-Methyl-3-(5,5,8,8-tetra-methyl-5,6,7,8-tetra-hydro-naphthalen-2-yl)-oxiranyl]-benzoic acid.

Related compounds are diketones, diols, and acetonides of the formula





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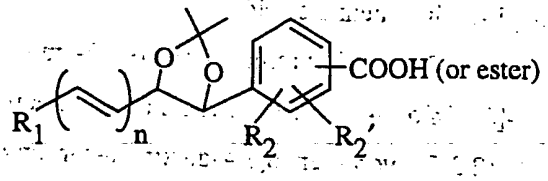
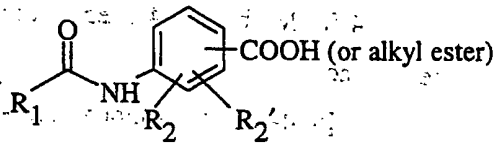
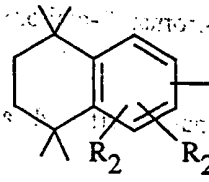


Certain retinoids have a carboxyamide linkage rather than an alkylene or oxidized alkylene. For example, carboxamide retinoids which can be utilized include those of the formula



where R_1 is an organic radical and includes groups such as



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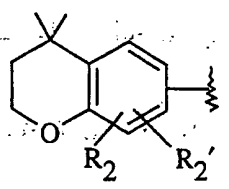

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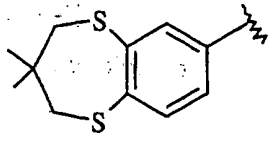

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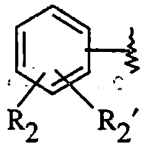

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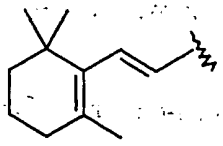

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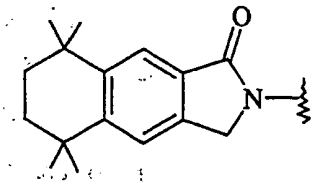

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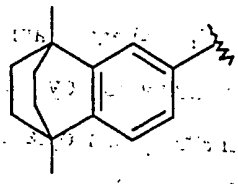

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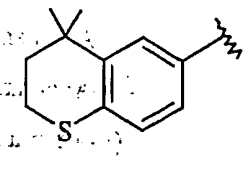


Typical carboxamide retinoids which can be utilized include:

4-benzoylamino-benzoic acid;

4-(3-tert-Butyl-benzoylamino)-benzoic acid;

4-(4-tert-Butyl-benzoylamino)-benzoic acid;

4-(3,5-Di-tert-butyl-benzoylamino)-benzoic acid;

4-(3,4-Diisopropyl-benzoylamino)-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-amino]-benzoic acid;

4-[Methyl-5,5,8,8-tetramethyl-5,6,7,8-tetra-hydro-naphthalene-2-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-chroman-7-carbonyl)-amino]-benzoic acid;

4-[(5-Chloro-4,4-dimethyl-chroman-7-carbonyl)-amino]-benzoic acid;

4-[(2,3-Dihydro-benzo[1,4]dioxine-6-carbonyl)-amino]-benzoic acid;

4-[(3,3-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-carbonyl)-amino]-benzoic acid;

4-[(5-Methyl-2,3,4,5-tetrahydro-benzo[b]thiepine-8-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-thiochroman-7-carbonyl)-amino]-benzoic acid

4-[(Thiochroman-6-carbonyl)-amino]-benzoic acid;

4-[(2,3-Dihydro-benzo[1,4]dithiine-6-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-1,1-dioxo-1l>6_-thiochroman-7-carbonyl)-amino]-benzoic acid;

4-[(3-Methyl-1,1-dioxo-1l>6_-thiochroman-6-carbonyl)-amino]-benzoic acid;

4-[(1,4,4-Trimethyl-1,2,3,4-tetrahydro-quinoline-7-carbonyl)-amino]-benzoic acid;

4-[(1-Decyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-7-carbonyl)-amino]-benzoic acid;

4-(3-tert-Butyl-4-methoxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-hydroxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-methoxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-methoxy-benzoylamino)-2-hydroxy-benzoic acid;

4-(3-Adamantan-1-yl-4-hexyloxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-decyloxy-benzoylamino)-benzoic acid;

4-[3-(1,1-Dimethyl-decyl)-4-methoxy-benzoylamino]-benzoic acid;

N-Phenyl-terephthalamic acid;

N-m-Tolyl-terephthalamic acid;

N-(3-Ethyl-phenyl)-terephthalamic acid;

N-(3-Isopropyl-phenyl)-terephthalamic acid;

N-(4-Isopropyl-phenyl)-terephthalamic acid;

N-(3-tert-Butyl-phenyl)-terephthalamic acid;

N-(4-tert-Butyl-phenyl)-terephthalamic acid;

N-(3-Cyclohexyl-phenyl)-terephthalamic acid;

N-Biphenyl-3-yl-terephthalamic acid;

N-(3-Bromo-phenyl)-terephthalamic acid;

N-(3-Dimethylamino-phenyl)-terephthalamic acid;

N-(3-Trifluoromethyl-phenyl)-terephthalamic acid;

N-(3,4-Diethyl-phenyl)-terephthalamic acid;

N-(2-Isopropyl-phenyl)-terephthalamic acid;

N-(2,4-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,5-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,6-Diisopropyl-phenyl)-terephthalamic acid;

N-(3,4-Diisopropyl-phenyl)-terephthalamic acid;

N-(3,5-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,4-Di-tert-butyl-phenyl)-terephthalamic acid;

N-(3,5-Di-tert-butyl-phenyl)-terephthalamic acid;

N-(3,4-Dichloro-phenyl)-terephthalamic acid;

N-(5,6,7,8-Tetrahydro-naphthalen-1-yl)-terephthalamic acid;

N-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-terephthalamic acid;

N-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

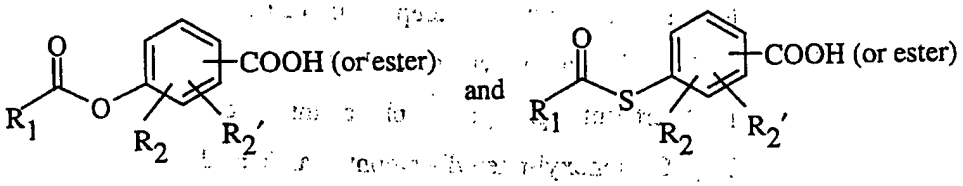
N-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-Methyl-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

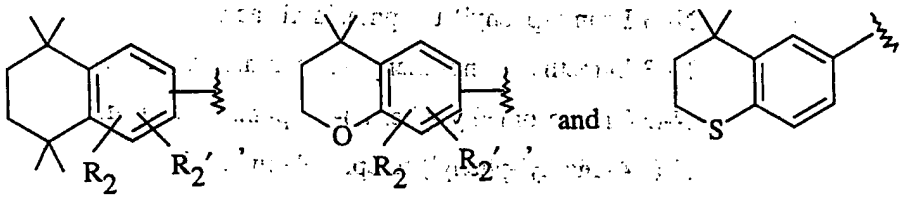
N-Isopropyl-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid; and

N-(3-Bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid.

Retinoids similar to the carboxamides are carboxy esters such as



for example, where R_1 includes



As noted before, any of these groups can be substituted in the ring system by R_2 and R_2', as well as by other art-recognized substituent groups.

Typical (aroyloxy) benzoic acids and thio acids which can be utilized include

Benzoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, carboxyphenyl ester;

Benzoic acid, 4-ethyl-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-ethenyl-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-methylphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-2-(hydroxymethyl)phenyl ester;

4-(4-Adamantan-1-yl-3-methoxy-benzoyloxy)-isophthalic acid;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-hydroxyphenyl ester;

Benzoic acid, 2,4-dimethoxy-5-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-2-methoxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-methoxyphenyl ester;

Benzoic acid, 2-fluoro-4-methoxy-5-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-fluorophenyl ester;

Benzoic acid, 4-(2-propenyloxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(acetyloxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(2-methoxy-2-oxoethoxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-[2-(phenylmethoxy)-2-oxoethoxy]-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(methylsulfonyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

4,4-Dimethyl-chroman-6-carboxylic acid;
4-ethoxycarbonyl-phenyl ester;

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid;
4-ethoxycarbonyl-phenyl ester;

2,2,4,4,7-Pentamethyl-chroman-6-carboxylic acid;
4-ethoxycarbonyl-phenyl ester;

4,4,7-Trimethyl-thiochroman-6-carboxylic acid;
4-ethoxycarbonyl-phenyl ester;

2,2,4,4-Tetramethyl-thiochroman-6-carboxylic acid;

4-ethoxycarbonyl-phenyl ester;

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonylsulfanyl)-benzoic acid;

4-(3-Isopropyl-4-methoxy-benzoylsulfanyl)-benzoic acid;

4-(3-Isopropylsulfanyl-4-methyl-benzoylsulfanyl)-benzoic acid;

4-(3-Adamantan-1-yl-benzoylsulfanyl)-benzoic acid;

4-(5-Adamantan-1-yl-2-fluoro-4-methoxy-benzoylsulfanyl)-benzoic acid;

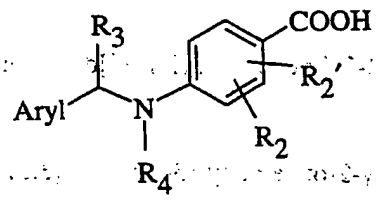
4-(5-Adamantan-1-yl-4-methoxy-2-methyl-benzoylsulfanyl)-benzoic acid;

4-(3-Adamantan-1-yl-4-allyloxy-benzoylsulfanyl)-benzoic acid;

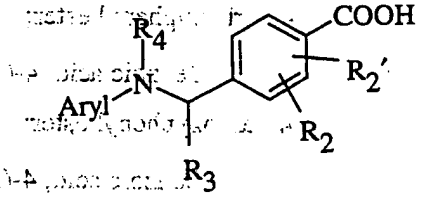
4-(3-Adamantan-1-yl-4-methylsulfanyl-benzoylsulfanyl)-benzoic acid; and

4-(3,5-Bis-trifluoromethyl-benzoylsulfanyl)-benzoic acid.

Other benzoic acid derivatives which are retinoids and which can be utilized to lower Lp(a) according to this invention include (arylmethyl)amino benzoic acid, for example, compounds of the formulas



and



where aryl is an aromatic radical such as phenyl, naphthyl, thienyl, or the like, optionally substituted with from 1 to 5 substituents such as alkyl, alkenyl, alkynyl, halo, nitro, amino, mono- or dialkylamino, hydroxy, and the like, and R_3 and R_4 are hydrogen, alkyl, alkenyl, alkynyl, or the like.

Typical aryl methylamino benzoic acid retinoids from this class include

4-(4-tert-Butyl-benzylamino)-benzoic acid;

4-(3,5-Di-tert-butyl-4-hydroxy-benzylamino)-benzoic acid;

4-(4-tert-Butoxy-3-methoxy-benzylamino)-benzoic acid;

4-[4-(1-Methoxy-1-methyl-ethyl)-benzylamino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(3-Fluoro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(1-Butoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,8-dihydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-7-oxo-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(7-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[1-(7-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-benzoic acid;

4-[Methyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[Acetyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5-tert-Butyl-2-methyl-phenylamino)-methyl]-benzoic acid;

4-[(3,5-Di-tert-butyl-phenylamino)-methyl]-benzoic acid;

4-[(4-tert-Butyl-2,6-dimethyl-phenylamino)-methyl]-benzoic acid;

4-[(1,1,2,3,3-Pentamethyl-indan-5-ylamino)-methyl]-benzoic acid;

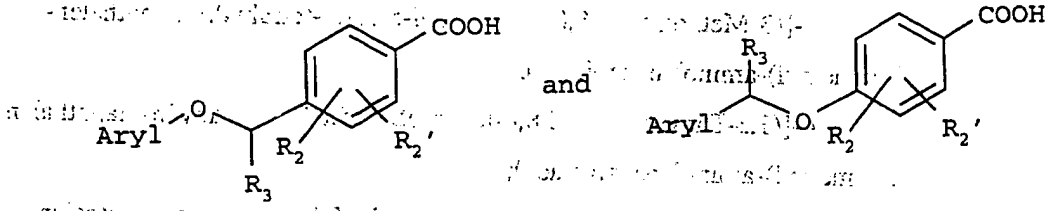
4-[1-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-ethyl]-benzoic acid;

4-[(1,4-Dichloro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-methyl]-benzoic acid;

4-[(1,4-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-methyl]-benzoic acid; and

4-{[Acetyl-(1,4-dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-amino]-methyl}-benzoic acid.

Another preferred group of retinoids that are effective in lowering Lp(a) include (aryloxy)methyl benzoic acid of the formulas



Typical members of this class include

4-(4-tert-Butyl-phenoxymethyl)-benzoic acid;

4-(3-tert-Butyl-phenoxymethyl)-benzoic acid;

4-[4-(1,1-Dimethyl-propyl)-phenoxymethyl]-benzoic acid;

4-(2-tert-Butyl-4-methyl-phenoxymethyl)-benzoic acid;

4-(4-tert-Butyl-2-methyl-phenoxymethyl)-benzoic acid;

4-(2,4-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,6-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,5-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(3,5-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2-sec-Butyl-4-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,4-Di-tert-butyl-5-methyl-phenoxymethyl)-benzoic acid;

4-(2,4,6-Tri-tert-butyl-phenoxymethyl)-benzoic acid;

4-(3,5-Di-tert-butyl-2-hydroxy-phenoxymethyl)-benzoic acid;

4-(5,5,8,8-Tetramethyl-3-nitro-5,6,7,8-tetrahydro-naphthalen-2-yloxymethyl)-benzoic acid;

4-(1,4-Dihydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxymethyl)-benzoic acid;

4-(1,4-Diacetoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxymethyl)-benzoic acid;

4-(2,2,5,7,8-Pentamethyl-chroman-6-yloxymethyl)-benzoic acid;

4-[2-(2-Hydroxy-ethyl)-2,5,7,8-tetramethyl-chroman-6-yloxymethyl]-benzoic acid; and

4-[2-(2-Acetoxy-ethyl)-2,5,7,8-tetramethyl-chroman-6-yloxymethyl]-benzoic acid.

Similar compounds which have sulfur in the linkage instead of oxygen include the following:

4-(4-tert-Butyl-phenylsulfanylmethyl)-benzoic acid;

4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid;

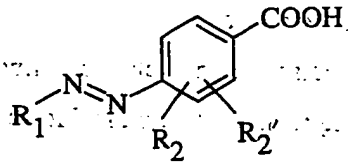
4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid;

4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid;

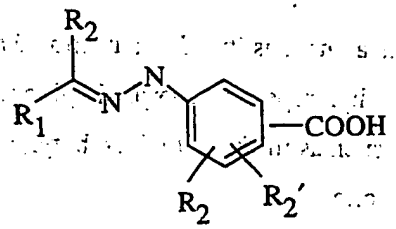
4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid; and

4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid.

Like the carboxamides and esters, some retinoids have more than one nitrogen in the linking chain, for example, there are arylazobenzoic acids such as



and hydrazone-bridge benzoic acids such as



Typical members of this class include:

4-(3,4-Diethyl-phenylazo)-benzoic acid;

4-(2-Isopropyl-phenylazo)-benzoic acid;

4-(3-Isopropyl-phenylazo)-benzoic acid;

4-(4-Isopropyl-phenylazo)-benzoic acid;

4-(2,4-Diisopropyl-phenylazo)-benzoic acid;

4-(2,6-Diisopropyl-phenylazo)-benzoic acid;

4-(3,4-Diisopropyl-phenylazo)-benzoic acid;

4-(3,5-Diisopropyl-phenylazo)-benzoic acid;

4-(3-tert-Butyl-phenylazo)-benzoic acid;

4-(3-Cyclohexyl-phenylazo)-benzoic acid;

4-(Biphenyl-3-ylazo)-benzoic acid;

4-(4,4-Dimethyl-thiochroman-6-ylazo)-benzoic acid;

4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-benzoic acid;

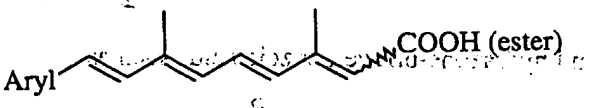
4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylsulfanyl]-benzoic acid;

4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethoxy]-benzoic acid;

4-[N'-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)-hydrazino]-benzoic acid; and

4-{N'-[Cyclopropyl-(1,1,2,3,3-pentamethyl-indan-5-yl)-methylene]-hydrazino}-benzoic acid.

A particular preferred class of retinoid compounds to be utilized to lower Lp(a) according to this invention include polyenoic acids and esters such as



where aryl is an unsubstituted or substituted aromatic or cyclic radical such as phenyl, naphthyl, piperidyl, morpholinyl, or the like, and ester is preferably an alkyl group such as methyl, ethyl, isobutyl, or the like. Typical polyenoic retinoids include the following:

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid methyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-(2-oxo-pyrrolidin-1-yl)-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-(2-oxo-pyrrolidin-1-yl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-piperidin-1-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-morpholin-4-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-piperidin-1-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(2,6-dioxo-cyclohexyl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-methanesulfonyl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid methoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid tert-butoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid phenoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-acetoxy-phenoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid styryloxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(4-methoxy-phenyl)-vinyloxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(benzoyl-carbonyl)-5-methoxy-phenoxymethoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 1-phenoxycarbonyl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 1-ethoxycarbonyloxy-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

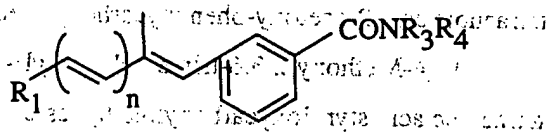
3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 4-dimethylamino-6-methyl-2-(2-octyl-hexadecyloxy)-tetrahydro-pyran-3-yl ester;

9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

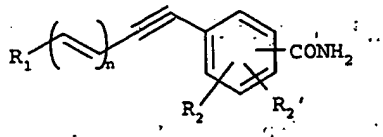
9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester; and

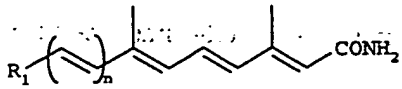
9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester.

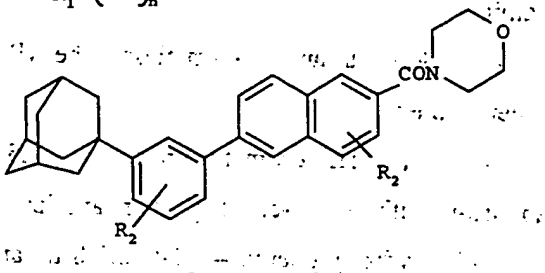
In addition to retinoic acids and esters, the method of this invention can be practiced with retinoid amides, for example, any of the foregoing compounds in an amide form, e.g., the general formula

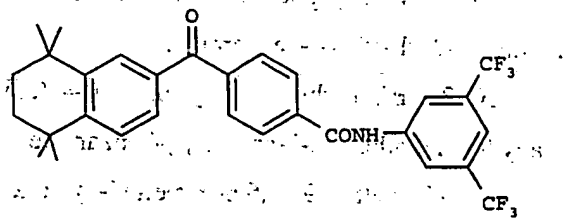


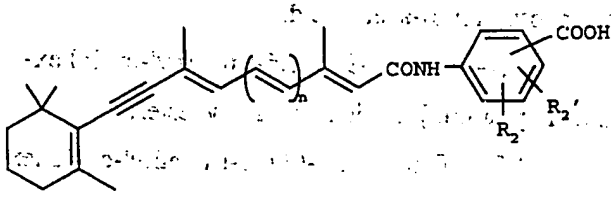
where R_3 and R_4 independently and hydrogen, C_1-C_6 alkyl, phenyl, or R_2R_2' substituted or disubstituted phenyl, or taken together with the nitrogen to which they are attached, R_3 and R_4 complete a ring which can have 1 or 2 heteroatoms, such as oxygen, sulfur, or nitrogen. Typical retinoids of this type include

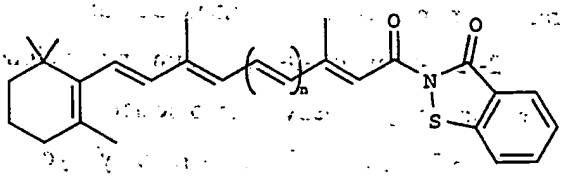


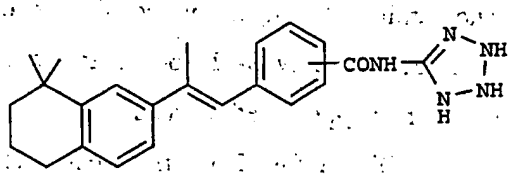


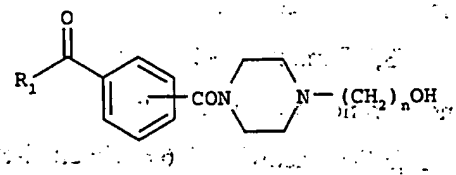


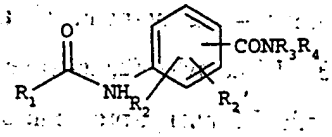












Examples of specific retinoids having the above structures include the following:

4-[4-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-3-en-1-ynyl]-benzamide;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid amide;

[6-(3-Adamantan-1-yl-4-methoxy-phenyl)-naphthalen-2-yl]-morpholin-4-yl-methanone;

N-(3,5-Bis-trifluoromethyl-phenyl)-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

N-(4-Hydroxy-phenyl)-4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzamide;

N-(3,5-Bis-trifluoromethyl-phenyl)-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid methyl ester;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-4-methyl-pentanoic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-phenyl-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-(4-hydroxy-phenyl)-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-pentanedioic acid;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-4-methyl-pentanoic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-phenyl-propionic acid;

tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone;

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid; [2-(2-hydroxy-ethoxy)-ethyl]-amide;

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid (4-hydroxy-phenyl)-amide;

4-Methylsulfanyl-2-{[6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carbonyl]-amino}-butyric acid;

5-(4-Adamantan-2-ylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoic acid (2-ethyl-hexyl)-amide;

2-[5-(4-Adamantan-2-ylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoylamino]-4-methylsulfanyl-butyric acid ethyl ester;

4-[2-(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-N-(2-hydroxy-ethyl)-benzamide;

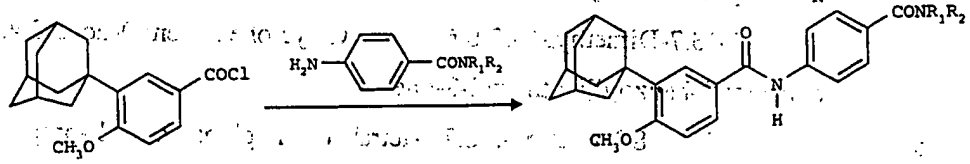
N-Butyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

N-(2-Hydroxy-ethyl)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide; and

{2-[4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl-carbonyl]-phenyl}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone.

An especially preferred group of retinoids for lowering Lp(a) are adamantyl substituted benzamides which can be prepared by reacting a compound

such as 3-adamantan-1-yl-4-methoxy-benzoyl chloride with a 4-aminobenzamide according to the following sequence



where R_1 and R_2 can be organic radicals such as C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and the like, or together with the nitrogen form a cyclic ring such as pyrrolidine or the like.

Typical amino benzamide starting materials include

4-Amino-N-tert-butyl-benzamide;

4-Amino-N-phenyl-benzamide;

4-Amino-N-benzyl-benzamide;

4-Amino-N-(2-hydroxy-ethyl)-benzamide;

(4-Amino-phenyl)-pyrrolidin-1-yl-methanone;

(4-Amino-phenyl)-piperidin-1-yl-methanone; and

(4-Amino-phenyl)-morpholin-4-yl-methanone.

Typical retinoids prepared as described above include

Benzamide, N-[4-[[(1,1-dimethylethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[(phenylamino)carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[[(phenylmethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[[(2-hydroxyethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

3-Adamantan-1-yl-4-methoxy-N-[4-(pyrrolidine-1-carbonyl-carbonyl)-phenyl]-benzamide;

3-Adamantan-1-yl-4-methoxy-N-[4-(piperidine-1-carbonyl-carbonyl)-phenyl]-benzamide; and

3-Adamantan-1-yl-4-methoxy-N-[4-(morpholine-4-carbonyl-carbonyl)-phenyl]-benzamide.

The following specific retinoids are also useful in the method of this invention:

4-[3-(4-tert-Butyl-phenyl)-oxiranyl]-benzoic acid;

4-[3-(3-tert-Butyl-phenyl)-oxiranyl]-benzoic acid;

4-[3-(3,4-Diethyl-phenyl)-3-methyl-oxiranyl]-benzoic acid;

4-[3-Methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-oxiranyl]-benzoic acid;

4-Benzoylamino-benzoic acid;

4-(3-tert-Butyl-benzoylamino)-benzoic acid;

4-(4-tert-Butyl-benzoylamino)-benzoic acid;

4-(3,5-Di-tert-butyl-benzoylamino)-benzoic acid;

4-(3,4-Diisopropyl-benzoylamino)-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-amino]-benzoic acid;

4-[Methyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-chroman-7-carbonyl)-amino]-benzoic acid;

4-[(5-Chloro-4,4-dimethyl-chroman-7-carbonyl)-amino]-benzoic acid;

4-[(2,3-Dihydro-benzo[1,4]dioxine-6-carbonyl)-amino]-benzoic acid;

4-[(3,3-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepine-7-carbonyl)-amino]-benzoic acid;

4-[(5-Methyl-2,3,4,5-tetrahydro-benzo[b]thiepine-8-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-thiochroman-7-carbonyl)-amino]-benzoic acid;

4-[(Thiochroman-6-carbonyl)-amino]-benzoic acid;

4-[(2,3-Dihydro-benzo[1,4]dithiine-6-carbonyl)-amino]-benzoic acid;

4-[(4,4-Dimethyl-1,1-dioxo-1l>6_-thiochroman-7-carbonyl)-amino]-benzoic acid;

4-[(3-Methyl-1,1-dioxo-1l>6_-thiochroman-6-carbonyl)-amino]-benzoic acid;

4-[(1,4,4-Trimethyl-1,2,3,4-tetrahydro-quinoline-7-carbonyl)-amino]-benzoic acid;

4-[(1-Decyl-4,4-dimethyl-1,2,3,4-tetrahydro-quinoline-7-carbonyl)-amino]-benzoic acid;

4-(3-tert-Butyl-4-methoxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-hydroxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-methoxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-methoxy-benzoylamino)-2-hydroxy-benzoic acid;

4-(3-Adamantan-1-yl-4-hexyloxy-benzoylamino)-benzoic acid;

4-(3-Adamantan-1-yl-4-decyloxy-benzoylamino)-benzoic acid;

4-[3-(1,1-Dimethyl-decyl)-4-methoxy-benzoylamino]-benzoic acid;

N-Phenyl-terephthalamic acid;

N-m-Tolyl-terephthalamic acid;

N-(3-Ethyl-phenyl)-terephthalamic acid;

N-(3-Isopropyl-phenyl)-terephthalamic acid;

N-(4-Isopropyl-phenyl)-terephthalamic acid;

N-(3-tert-Butyl-phenyl)-terephthalamic acid;

N-(4-tert-Butyl-phenyl)-terephthalamic acid;

N-(3-Cyclohexyl-phenyl)-terephthalamic acid;

N-Biphenyl-3-yl-terephthalamic acid;

N-(3-Bromo-phenyl)-terephthalamic acid;

N-(3-Dimethylamino-phenyl)-terephthalamic acid;

N-(3-Trifluoromethyl-phenyl)-terephthalamic acid;

N-(3,4-Diethyl-phenyl)-terephthalamic acid;

N-(2-Isopropyl-phenyl)-terephthalamic acid;

N-(2,4-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,5-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,6-Diisopropyl-phenyl)-terephthalamic acid;

N-(3,4-Diisopropyl-phenyl)-terephthalamic acid;

N-(3,5-Diisopropyl-phenyl)-terephthalamic acid;

N-(2,4-Di-tert-butyl-phenyl)-terephthalamic acid;

N-(3,5-Di-tert-butyl-phenyl)-terephthalamic acid;

N-(3,4-Dichloro-phenyl)-terephthalamic acid;

N-(5,6,7,8-Tetrahydro-naphthalen-1-yl)-terephthalamic acid;

N-(5,6,7,8-Tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-1-yl)-terephthalamic acid;

N-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-Methyl-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-Isopropyl-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(3-Bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(3-Amino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(5,5,8,8-Tetramethyl-3-nitro-5,6,7,8-tetrahydro-naphthalen-2-yl)-terephthalamic acid;

N-(4,4-Dimethyl-chroman-6-yl)-terephthalamic acid;

N-(4,4-Dimethyl-thiochroman-6-yl)-terephthalamic acid;

Benzoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, carboxyphenyl ester;

Benzoic acid, 4-ethyl-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-ethenyl-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-methylphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-2-(hydroxymethyl)phenyl ester;

4-(4-Adamantan-1-yl-3-methoxy-benzoyloxy)-isophthalic acid;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-hydroxyphenyl ester;

Benzoic acid, 2,4-dimethoxy-5-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-2-methoxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-methoxyphenyl ester;

Benzoic acid, 2-fluoro-4-methoxy-5-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxy-3-fluorophenyl ester;

Benzoic acid, 4-(2-propenyloxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(acetyloxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(2-methoxy-2-oxoethoxy)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-[2-(phenylmethoxy)-2-oxoethoxy]-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

Benzoic acid, 4-(methylsulfonyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-, 4-carboxyphenyl ester;

4,4-Dimethyl-chroman-6-carboxylic acid 4-ethoxycarbonyl-phenyl ester;

2,2,4,4-Tetramethyl-chroman-6-carboxylic acid 4-ethoxycarbonyl-phenyl ester;

2,2,4,4,7-Pentamethyl-chroman-6-carboxylic acid 4-ethoxycarbonyl-phenyl ester;

4,4,7-Trimethyl-thiochroman-6-carboxylic acid 4-ethoxycarbonyl-phenyl ester;

2,2,4,4-Tetramethyl-thiochroman-6-carboxylic acid 4-ethoxycarbonyl-phenyl ester;

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonylsulfanyl)-benzoic acid;

4-(3-Isopropyl-4-methoxy-benzoylsulfanyl)-benzoic acid;

4-(3-Isopropylsulfanyl-4-methyl-benzoylsulfanyl)-benzoic acid;

4-(3-Adamantan-1-yl-benzoylsulfanyl)-benzoic acid;

4-(5-Adamantan-1-yl-2-fluoro-4-methoxy-benzoylsulfanyl)-benzoic acid;

4-(5-Adamantan-1-yl-4-methoxy-2-methyl-benzoylsulfanyl)-benzoic acid;

4-(3-Adamantan-1-yl-4-allyloxy-benzoylsulfanyl)-benzoic acid;

4-(3-Adamantan-1-yl-4-methylsulfanyl-benzoylsulfanyl)-benzoic acid;

4-(3,5-Bis-trifluoromethyl-benzoylsulfanyl)-benzoic acid;

4-(4-tert-Butyl-benzylamino)-benzoic acid;

4-(3,5-Di-tert-butyl-4-hydroxy-benzylamino)-benzoic acid;

4-(4-tert-Butoxy-3-methoxy-benzylamino)-benzoic acid;

4-[4-(1-Methoxy-1-methyl-ethyl)-benzylamino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(3-Fluoro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(1-Butoxy-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-5,8-dihydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5,5,8,8-Tetramethyl-7-oxo-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(7-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[1-(7-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-benzoic acid;

4-[Methyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[Acetyl-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-amino]-benzoic acid;

4-[(5-tert-Butyl-2-methyl-phenylamino)-methyl]-benzoic acid;

4-[(3,5-Di-tert-butyl-phenylamino)-methyl]-benzoic acid;

4-[(4-tert-Butyl-2,6-dimethyl-phenylamino)-methyl]-benzoic acid;

4-[(1,1,2,3,3-Pentamethyl-indan-5-ylamino)-methyl]-benzoic acid;

4-[1-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-ethyl]-benzoic acid;

4-[(1,4-Dichloro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-methyl]-benzoic acid;

4-[(1,4-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylamino)-methyl]-benzoic acid;

4-{[Acetyl-(1,4-dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-amino]-methyl}-benzoic acid;

4-(4-tert-Butyl-phenoxymethyl)-benzoic acid;

4-(3-tert-Butyl-phenoxymethyl)-benzoic acid;

4-[4-(1,1-Dimethyl-propyl)-phenoxymethyl]-benzoic acid;

4-(2-tert-Butyl-4-methyl-phenoxymethyl)-benzoic acid;

4-(4-tert-Butyl-2-methyl-phenoxymethyl)-benzoic acid;

4-(2,4-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,6-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,5-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(3,5-Di-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2-sec-Butyl-4-tert-butyl-phenoxymethyl)-benzoic acid;

4-(2,4-Di-tert-butyl-5-methyl-phenoxymethyl)-benzoic acid;

4-(2,4,6-Tri-tert-butyl-phenoxymethyl)-benzoic acid;

4-(3,5-Di-tert-butyl-2-hydroxy-phenoxymethyl)-benzoic acid;

4-(5,5,8,8-Tetramethyl-3-nitro-5,6,7,8-tetrahydro-naphthalen-2-yloxymethyl)-benzoic acid;

4-(1,4-Dihydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxymethyl)-benzoic acid;

4-(4-tert-Butyl-2-methyl-phenylsulfanylmethyl)-benzoic acid;

4-(3,4-Diethyl-phenylazo)-benzoic acid;

4-(2-Isopropyl-phenylazo)-benzoic acid;

4-(3-Isopropyl-phenylazo)-benzoic acid;

4-(4-Isopropyl-phenylazo)-benzoic acid;

4-(2,4-Diisopropyl-phenylazo)-benzoic acid;

4-(2,6-Diisopropyl-phenylazo)-benzoic acid;

4-(3,4-Diisopropyl-phenylazo)-benzoic acid;

4-(3,5-Diisopropyl-phenylazo)-benzoic acid;

4-(3-tert-Butyl-phenylazo)-benzoic acid;

4-(3-Cyclohexyl-phenylazo)-benzoic acid;

4-(Biphenyl-3-ylazo)-benzoic acid;

4-(4,4-Dimethyl-thiochroman-6-ylazo)-benzoic acid;

4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-benzoic acid;

4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylsulfanyl]-benzoic acid;

4-[2-Hydroxy-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-ethoxy]-benzoic acid;

4-[N'-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)-hydrazino]-benzoic acid;

4-{N'-[Cyclopropyl-(1,1,2,3,3-pentamethyl-indan-5-yl)-methylene]-hydrazino}-benzoic acid;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-(2-oxo-pyrrolidin-1-yl)-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-(2-oxo-pyrrolidin-1-yl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethoxy}-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-piperidin-1-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-etraenoic acid 2-morpholin-4-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-piperidin-1-yl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(2,5-dioxo-pyrrolidin-1-yl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(2,6-dioxo-cyclohexyl)-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-methanesulfonyl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid methoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid tert-butoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid phenoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-acetoxy-phenoxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid styryloxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(4-methoxy-phenyl)-vinyloxycarbonylmethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-(benzoyl-carbonyl)-5-methoxy-phenoxymethoxycarbonyl-methyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 1-phenoxycarbonyl-ethyl ester;

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 1-ethoxycarbonyloxy-ethyl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid 4-dimethylamino-6-methyl-2-(2-octyl-hexadecyloxy)-tetrahydro-pyran-3-yl ester;

9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

9-(4-Methoxy-2,5,6-trimethyl-cyclohex-1-enyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoic acid 2-butoxy-4-dimethylamino-6-methyl-tetrahydro-pyran-3-yl ester;

4-[4-(2,6,6-Trimethyl-cyclohex-1-enyl)-but-3-en-1-ynyl]-benzamide;

3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid amide;

[6-(3-Adamantan-1-yl-4-methoxy-phenyl)-naphthalen-2-yl]-morpholin-4-yl-methanone;

N-(3,5-Bis-trifluoromethyl-phenyl)-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

N-(4-Hydroxy-phenyl)-4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzamide;

N-(3,5-Bis-trifluoromethyl-phenyl)-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-4-methyl-pentanoic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-phenyl-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-(4-hydroxy-phenyl)-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-pentanedioic acid;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-propionic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-4-methyl-pentanoic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-3-phenyl-propionic acid;

4-[3,7-Dimethyl-9-(3,3,6,6-tetramethyl-cyclohex-1-enyl)-nona-2,4,6-trien-8-ynoylamino]-benzoic acid;

2-[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoyl]-benzo[d]isothiazol-3-one;

4-[2-(8,8-Dimethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-N-(1H-tetrazol-5-yl)-benzamide;

[3,7-Dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoylamino]-acetic acid;

4-Methyl-7-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-octa-2,4,6-trienoic acid ethylamide;

{4-[4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl]-phenyl}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone;

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide;

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carboxylic acid (4-hydroxy-phenyl)-amide;

4-Methylsulfanyl-2-{[6-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-naphthalene-2-carbonyl]-amino}-butyric acid;

5-(4-Adamantan-2-ylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoic acid (2-ethyl-hexyl)-amide;

2-[5-(4-Adamantan-2-ylidenemethyl-phenyl)-3-methyl-penta-2,4-dienoylamino]-4-methylsulfanyl-butyric acid ethyl ester;

4-[2-(1,3-Dimethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-N-(2-hydroxy-ethyl)-benzamide;

N-Butyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

N-(2-Hydroxy-ethyl)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carbonyl)-benzamide;

{2-[4-(2-Hydroxy-ethyl)-piperazine-1-carbonyl-carbonyl]-phenyl}-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone;

3-Adamantan-1-yl-4-methoxy-benzoyl chloride;

4-Amino-N-tert-butyl-benzamide;

4-Amino-N-phenyl-benzamide;

4-Amino-N-benzyl-benzamide;

4-Amino-N-(2-hydroxy-ethyl)-benzamide;

(4-Amino-phenyl)-pyrrolidin-1-yl-methanone;

(4-Amino-phenyl)-piperidin-1-yl-methanone;

(4-Amino-phenyl)-morpholin-4-yl-methanone;

Benzamide, N-[4-[[(1,1-dimethylethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[(phenylamino)carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[[(phenylmethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

Benzamide, N-[4-[[(2-hydroxyethyl)amino]carbonyl]phenyl]-4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-;

3-Adamantan-1-yl-4-methoxy-N-[4-(pyrrolidine-1-carbonyl-carbonyl)-phenyl]-benzamide;

3-Adamantan-1-yl-4-methoxy-N-[4-(piperidine-1-carbonyl-carbonyl)-phenyl]-benzamide;

3-Adamantan-1-yl-4-methoxy-N-[4-(morpholine-4-carbonyl-carbonyl)-phenyl]-benzamide;

1,1,3,3-Tetramethyl-5-(1-methyl-2-phenyl-vinyl)-indan;

6-(1-Methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

6-(1-Methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

1,1-Dimethyl-6-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

1,1,4,4-Tetramethyl-6-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

1,1,4,4,6-Pentamethyl-7-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

1,1,4,4-Tetramethyl-6-(1-methyl-2-phenyl-vinyl)-7-octyl-1,2,3,4-tetrahydro-naphthalene;

6-Methoxy-1,1,4,4-tetramethyl-7-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

6-Chloro-1,1,4,4-tetramethyl-7-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

(Z)-1,1,4,4-Tetramethyl-6-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalene;

1,1,4,4-Tetramethyl-6-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalen-2-ol;

1,1,4,4,6-Pentamethyl-7-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-naphthalen-2-ol;

1,1,3,3-Tetramethyl-5-(1-methyl-2-phenyl-vinyl)-indan-2-one;

1,4,4-Trimethyl-7-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-quinoline;

1,4,4-Trimethyl-6-(1-methyl-2-phenyl-vinyl)-1,2,3,4-tetrahydro-quinoline;

4,4-Dimethyl-7-(1-methyl-2-phenyl-vinyl)-chroman;

4,4-Dimethyl-6-(1-methyl-2-phenyl-vinyl)-chroman;

4,4-Dimethyl-7-(1-methyl-2-phenyl-vinyl)-thiochroman;

4,4-Dimethyl-6-(1-methyl-2-phenyl-vinyl)-thiochroman;

4,4-Dimethyl-7-(1-methyl-2-phenyl-vinyl)-thiochroman 1,1-dioxide;

4,4-Dimethyl-6-(1-methyl-2-phenyl-vinyl)-thiochroman 1,1-dioxide;

2,2-Dimethyl-5-(1-methyl-2-phenyl-vinyl)-benzo[1,3]dithiole;

7,7-Dimethyl-2-(1-methyl-2-phenyl-vinyl)-7,8-dihydro-6H-5,9-dithia-benzocycloheptene;

1,1,3,3-Tetramethyl-indan-5-carboxylic acid phenylamide;

5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid phenylamide;

5,5,7,7,9,9-Hexamethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylic acid phenylamide;

N-(1,1,3,3-Tetramethyl-indan-5-yl)-benzamide;

N-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzamide;

3-Adamantan-1-yl-4-methoxy-benzoic acid phenyl ester;

3-Adamantan-1-yl-4-methoxy-thiobenzoic acid S-phenyl ester;

4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenol;

Acetic acid 4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl ester;

1-(2-{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenoxy}-ethyl)-piperidine;

4-(2-{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenoxy}-ethyl)-morpholine;

4-(2-{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenoxy}-ethyl)-thiomorpholine 1,1-dioxide;

4-[2-(3-Chloro-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenol;

4-[2-(6-Methoxy-1,1,3,3-tetramethyl-indan-5-yl)-propenyl]-phenol;

5-[2-(4-Hydroxy-phenyl)-1-methyl-vinyl]-1,1,3,3-tetramethyl-indan-2-one;

5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (4-hydroxy-phenyl)-amide;

7,7-Dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylic acid (4-hydroxy-phenyl)-amide;

3-Ethyl-7,7-dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylic acid (4-hydroxy-phenyl)-amide;

4-Hydroxy-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzamide;

3-Adamantan-1-yl-4-methoxy-benzoic acid 4-hydroxy-phenyl ester;

3-Adamantan-1-yl-4-methoxy-thiobenzoic acid S-(4-hydroxy-phenyl) ester;

5-[2-Methyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-buta-1,3-dienyl]-1H-tetrazole;

5-{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-1H-tetrazole;

5-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylethynyl)-phenyl]-1H-tetrazole;

Methyl-{4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-phosphinic acid ethyl ester;

Phenyl-{4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-phosphinic acid ethyl ester;

{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-phosphonic acid dimethyl ester;

{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-phosphonic acid diethyl ester;

{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-phosphonic acid dibutyl ester;

{4-[2-(1,1,2,3,3-Pentamethyl-indan-5-yl)-propenyl]-phenyl}-phosphonic acid diethyl ester;

6-(2-Biphenyl-4-yl-1-methyl-vinyl)-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(2-Fluoro-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(2-Fluoro-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(4-Chloro-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(2-Bromo-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(3-Bromo-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

6-[2-(4-Iodo-phenyl)-1-methyl-vinyl]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene;

1,1,4,4-Tetramethyl-6-[1-methyl-2-(4-nitro-phenyl)-vinyl]-1,2,3,4-tetrahydro-naphthalene;

1,1,3,3-Tetramethyl-indan-5-carboxylic acid (4-fluoro-phenyl)-amide;

5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-naphthalene-2-carboxylic acid (4-fluoro-phenyl)-amide;

9,9-Dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylic acid (4-fluoro-phenyl)-amide;

7,7-Dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene-2-carboxylic acid (4-fluoro-phenyl)-amide;

4-Fluoro-N-(1,1,3,3-tetramethyl-indan-5-yl)-benzamide;

4-Fluoro-N-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzamide;

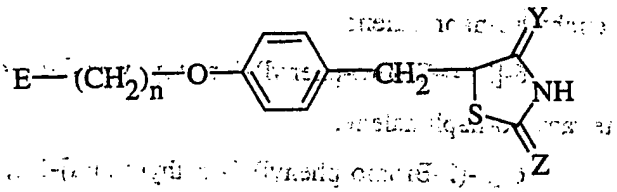
N>1_,N>1_-Dimethyl-N>2_-{4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-ethane-1,2-diamine;

Methyl-(2-morpholin-4-yl-ethyl)-{4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-propenyl]-phenyl}-amine;

6-{2-[4-(2-Methoxy-ethylsulfanyl)-phenyl]-1-methyl-vinyl}-1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene; and

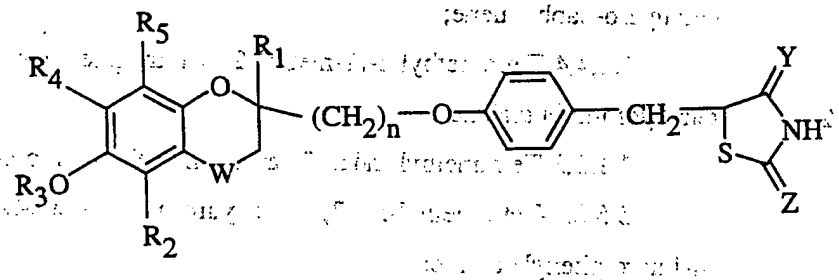
1,1,4,4-Tetramethyl-6-{1-methyl-2-[4-(2-methylsulfanyl-ethylsulfanyl)-phenyl]-vinyl}-1,2,3,4-tetrahydronaphthalene.

The glitazones are a family of antidiabetic agents characterized as being thiazolidinediones or related analogs. They are described in *Current Pharmaceutical Design*, 1996;2:85-101. Typical glitazones have the formula



where n is 1, 2, or 3, Y and Z independently are O or NH; and E is a cyclic or bicyclic aromatic or non-aromatic ring, optionally containing a heteroatom selected from oxygen or nitrogen.

Preferred glitazones have the formula



wherein:

R^1 and R^2 independently are hydrogen or C_1-C_5 alkyl;

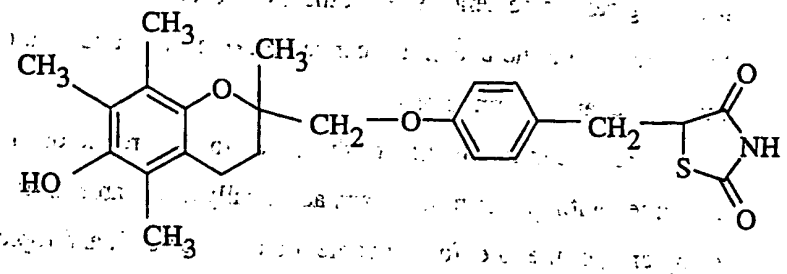
R^3 is hydrogen, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C_1-C_6 alkoxy) carbonyl group, or an aralkyloxycarbonyl group;

R^4 and R^5 independently are hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, or R^4 and R^5 together are C_1-C_4 alkylenedioxy;

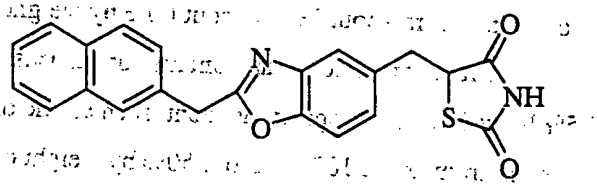
W is $-CH_2-$, $>CO$, or $CHOR^6$, where R^6 is any one of the atoms or groups defined for R^3 and may be the same as or different from R^3;

n, Y, and Z are as defined above, and pharmaceutically acceptable salts thereof.

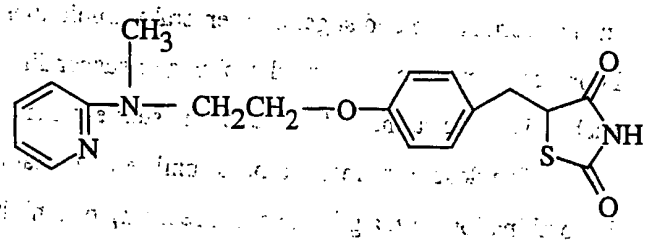
An especially preferred glitazone is troglitazone having the formula



Other glitazones that can be employed in this invention are described in United States Patent Numbers 5,457,109 and 5,478,852, which are incorporated herein by reference. Other specific glitazones which are preferred include ciglitazone, pioglitazone, englitazone, TA 174, which has the formula



and BRL 49653 (rosiglitazone), which has the formula



Additionally preferred glitazones include:

5-(4-[2-[1-(4-2′-Pyridylphenyl)ethylideneaminooxy]ethoxy]benzyl]-thiazolidine-2,4-dione;

5-(4-[5-Methoxy-3-methylimidazo[5,4-b]pyridin-2-yl]-methoxy)benzyl]thiazolidine-2,4-dione, or its hydrochloride;

5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)benzyl]-thiazolidine-2,4-dione;

5-[4-(1-Methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione; and

5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione.

The combinations of this invention will be used to inhibit cell proliferation, and thus to treat diseases which result from cell proliferation, including cancer, restenosis, and atherosclerosis. Cancers to be treated according to this invention include breast cancer, leukemias, ovarian, colon, pancreatic, melanoma, and lymphnomas.

For use in the method of this invention, the retinoids preferably are combined with one or more pharmaceutically acceptable diluents, carriers, excipients, or the like, for convenient oral, parenteral, and topical administration to animals, preferably humans. The retinoids are ideally suited to formulation for oral administration in the form of tablets, capsules, dispersible powders, granules, suspensions, elixirs, buccal seals, and the like. The formulations typically will contain from about 1% to about 90% by weight of active retinoid, and more commonly from about 5% to about 60% by weight.

Oral formulations can contain, for suspensions, from about 0.05% to about 5% by weight of a suspending agent, such as talc or the like, and syrups will contain from about 10% to about 50% by weight of a sugar such as dextrose. Tablets may contain normal amounts of binders, stabilizers, and common diluents such as corn starch and sugars. Parenteral formulations, for instance, solutions for IV injection, will be made by dissolving or suspending the retinoid in a solvent such as isotonic saline or 5% glucose in sterile water.

The dose of retinoid to be administered is that amount which is effective, in combination with a glitazone, for reducing or inhibiting cell proliferation.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, and the severity of the condition being treated. However, in general, satisfactory results are obtained when the retinoids are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained-release form. For most large mammals, such as humans, the total daily dosage is form about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid

pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The glitazones will likewise be formulated in their normal clinical dosage forms which are employed in treating non-insulin dependent diabetes mellitus, and impaired glucose tolerance. For example, troglitazone is routinely used at doses of about 200 to about 800 mg per day orally. Rosiglitazone will be used at about 2 to about 20 mg per day, typically about 5 to 8 mg. Pioglitazone generally will be administered orally at doses from about 5 to about 100 mg per day, more typically at about 10 to about 50 mg per day.

Both the retinoids and the glitazones may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose, and kaolin, while liquid carriers include sterile water, polyethylene glycols, nonionic surfactants, and edible oils such as corn, peanut, and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT, and BHA.

The preferred pharmaceutical compositions from the stand point of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. The retinoids and glitazones can be administered separately, for example as separate tablets, or they can be formulated together in a fixed dosage combination.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils.

Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds may also be encapsulated in liposomes to allow an intravenous administration of the drug. The liposomes suitable for use in the invention are lipid vesicles and may include plurilamellar lipid vesicles, small sonicated multimellar vesicles, reverse phase evaporation vesicles, large multilamellular vesicles, and the like, wherein the lipid vesicles are formed by one or more phospholipids such as phosphotidylcholine, phosphatidylglycerol, sphingomyelin, phospholactic acid, and the like. In addition, the liposomes may also comprise a sterol component such as cholesterol.

Some typical formulations which can be administered to humans are as follows:

Tablet Formulation

4-[2-(3,4-di-n-butylphenyl)-propenyl]-benzoic acid (250 mg) is blended to uniformity with 100 mg of corn starch and 50 mg of lactose. The mixture is compressed into a tablet. Such tablets are administered orally at the rate of one to three times a day.

Fixed Combination Tablet

Troglitazone (400 mg) and 9-cis-retinoic acid (50 mg) are blended with N-vinylpyrrolidone polymer and extruded at 180°C through a twin-screw extender to provide an extrudate which is compressed into a tablet.

Fixed Combination Tablet

Rosiglitazone (8 mg) and 13-cis-retinol (80 mg) are blended with 200 mg of corn starch and pressed into a tablet.

Preparation of Oral Suspension

Ingredient	Amount
4,4-dimethyl-7-(1-methyl-2-phenylvinyl)chroman	500 mg
Pioglitazone	35 mg
Sorbitol solution (70% NF)	40 mL
Sodium benzoate	150 mg
Saccharin	10 mg
Red dye	10 mg
Cherry flavor	50 mg
Distilled water qs OD	100 mL

The sorbitol solution is added to 40 mL of distilled water and the retinoid and glitazone are suspended thereon. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 2 mg of retinoid and 0.35 mg of pioglitazone.

Suppositories

A mixture of 300 mg of 4-(2,4-diisopropylbenzoyl)benzoic acid, 200 mg of troglitazone, and 500 mg of theobroma oil is stirred at 60°C to uniformity. The mixture is cooled and allowed to harden in a tapered mold to provide a 1-g suppository.

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of sterile water is suspended 20.0 g of retinoic acid and 5.0 g of rosiglitazone. The pH is adjusted to pH 6.5 with dilute sodium hydroxide, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0-mL ampoules each containing 2.0 mL, and sealed under nitrogen.

Preferred formulations are those incorporating any of the preferred retinoids and glitazones to be utilized to inhibit cell proliferation and thus to treat cancer, restenosis and atherosclerosis, and similar vascular smooth muscle cell proliferations. Specifically preferred are all trans isomers of retinoic acid, retinal, and retinol. Also preferred are the 9-cis isomers of retinoic acid, retinal, and retinol, as well as the 13-cis isomers of retinoic acid, retinal, and retinol. Certain retinoid esters also are preferred, for example, 3,7-dimethyl-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,6,8-tetraenoic acid, methyl ester.

When the retinoid and glitazone are formulated together, the compositions will contain about one to about 1000 parts by weight of retinoid, and about 1000 to about one part by weight glitazone. For example, a typical composition of 9-cis-RA and troglitazone will contain about 12 mg of 9-cis-RA and about 500 mg of troglitazone. Such combination will be administered to an adult patient about once each day to achieve a synergistic control of cell proliferation.

The compositions may contain common excipients and carriers such as starch, sucrose, talc, gelatin, methylcellulose, and magnesium stearate. The compositions will normally be made for oral administration, for instance as tablets or capsules, but also may be in the form of aqueous suspensions or solutions, suppositories, slow release forms, for example employing an osmotic pump, skin patch, or the like.

The ability of the retinoid-glitazone combinations to inhibit cell proliferation and thereby treat cancer has been established in experimental protocols. The following examples illustrate the surprising biological effects of the combinations.

EXAMPLE 1

PPARs exist heterodimerized to retinoid X receptor (RXR) on a gene's promoter peroxisome proliferator responsive element (PPRE). The consensus PPRE corresponds to a hexanucleotide direct repeat sequence separated by one nucleotide. The RXR ligand, 9-cis-RA, a natural derivative of vitamin A, cannot only activate signaling pathways through PPAR-RXR heterodimer, but also can mediate transactivation through LXR-RXR heterodimers and RXR-RXR homodimers. Clinically, retinoic acid derivatives have been widely used to supplement cancer treatment with variable outcomes. Indeed, utility of retinoids as cancer treatment has been suggested nearly 100 years ago. Perhaps, variation in the ability of retinoids to suppress tumors may be dependent on PPARγ expression and the presence of natural ligands to PPARγ. Therefore, it would be of interest to determine whether PPAR and RXR ligands might cooperate to suppress cell proliferation.

In the current study, RA treatment of human THP-1 monocytic leukemia cells induces expression of PPARγ1 RNA and protein. Under these conditions, RA caused a concentration dependent suppression of cell growth. At the lower concentrations, where RA was marginally effective in suppressing cell growth, the simultaneous treatment of the cells with BRL 49653 completely blocked cell proliferation. Treatment with BRL 49653 alone was ineffective. These results demonstrate RA induces expression of PPARγ1, and in the presence of their ligands, PPARγ1 and RXR cooperate to suppress cell growth. This interaction establishes the combinations are useful for growth suppression in other proliferative conditions (e.g., cancer, restenosis) when PPARγ is not highly expressed.

MATERIALS AND METHODS

Cell Culture and Differentiation. Human THP-1 cells were obtained from the American type Culture Collection (Rockville, MD). Cells were cultured in RPMI 1640 medium (GIBCO BRL) containing 10% fetal bovine serum, 0.05 mM 2-mercaptoethanol (GIBCO BRL). For RA treatment and macrophage

differentiation, cells were switched to differentiation medium (DM) containing 1% Nutridoma-Hu (Boehringer Mannheim), 0.05 mM 2-mercaptoethanol in RPMI 16140 medium with the addition of either RA or PMA in dimethylsulfoxide (DMSO) (0.2% of final volume).

Rhase Protection Assays. Total cellular RNA was isolated from THP-1 cells using Trizol reagents (GIBCO BRL). The cDNA probe for the human PPARγ was prepared by reverse transcription-polymerase chain reaction with primers generated from published sequences. The sequences of 5′- and 3′-oligonucleotides used were GACTGCAAGGACATGAGCGA (nucleotides 111-134) and CGGTTGGTGAAGAGCAGATA (nucleotides 251-274), respectively. Thus, a partial cDNA containing nucleotides 111-274 of hPPARγ2 was subcloned into the pCRII vector (Invitrogen). A labeled antisense riboprobe was synthesized using a Maxiscript in vitro transcription kit (Ambion). RNase protection assays were done with an Ambion RPA II RNase protection assay kit.

Western Blot Analysis. To detect the PPARγ protein, nuclear extracts were isolated as described by Andrews et al. for western blot analysis, *Nucleic Acids Res.*, 1991;19:2499. Protein concentrations were measured using Bio-Rad Protein Assay Reagent (Bio-Rad Laboratories, CA) following the manufacturer's suggested procedure. Protein was separated on a 6% Tris-Glycine gel (Novex). After electrophoresis, gels were transferred to nitrocellulose membranes and blocked overnight in PBST with 10% non-fat dry milk (Bio-Rad Laboratories, CA) at 4°C. Protein was detected using ECL western blotting analysis system (Amersham) following the manufacturer's suggested procedure. The primary antibody for PPARγ was a polyclonal antibody generated with the PPARγ C-terminal as epitope.

Flow Cytometry Cell Cycle Analysis. THP-1 cells treated with RA for 1 day were harvested and fixed with ice-cold 70% ethanol. The cells were then stained with a propidium iodide solution (100 μM in Dulbecco's-PBS w Ca^{2+}, Mg^{2+}, with 36U RNase A) and subjected to flow cytometry analysis on FACScan

(Becton Dickinson) following the manufacturer's suggested procedure. Data were analyzed using ModFit software (Verity Software House, Inc.).

CD14 and CD15 Immunocytometry Analysis. THP-1 cells were treated for one day with DMSO vehicle or RA, and then harvested and incubated with 10% heat-inactivated human serum (Sigma) to block cell membrane Fc receptors. After first staining with either α-CD14 (Ancell) or a mouse isotype antibody control (IgG2a), or α-CD15 (Ancell) or a mouse isotype antibody control (IgM). Cells were then treated with a propidium iodide solution and subjected to FACScan (Becton Dickinson) immunocytometry analysis. The FACScan histogram data were analyzed by CellQuest software (Becton Dickinson).

RESULTS

In the course of studying the regulation of PPARγ expression in human THP-1 monocytes, various stimulators were used, including the 9-cis-RA. It was found that growth suppression was induced in the THP-1 cells treated with RA alone. When cells were treated with DMSO vehicle alone, cell number increased nearly two-fold after 2 days in culture. Retinoic acid caused a concentration dependent suppression of cell growth, with near complete growth arrest at the highest concentration (500 nM) (Figure 1). At 500 nM RA, RNase protection analysis revealed PPARγ1 was upregulated in the RA-treated cells (Figure 2A). THP-1 cells treated with various concentration of RA demonstrated PPARγ1 expression increased in a concentration dependent fashion (Figure 2B, top panel). The nuclear PPARγ1 protein level (Figure 2B, bottom panel) paralleled the induction of PPARγ1 message (Figure 2B, top panel).

To determine whether growth arrest was dependent on ligand interaction with PPARγ1, cells were grown in the presence of BRL 49653 alone (Figure 3A) or in combination with a low concentration of RA (Figure 3B). BRL 49653 at 1 μM (Figure 3A) had only a modest effect of decreasing cell growth by 16% after 2 days. At 10 μM, BRL 49653 cell proliferation was inhibited by 55% after 2 days. At 5 nM RA alone (Figure 3B), cell growth was inhibited by 49% after

2 days. However, the simultaneous treatment of cells with both 5 nM RA plus 1 μM or 10 μM BRL 49653 caused a 64% and 100% inhibition in cell growth, respectively (Figure 3B). Flow cytometry analysis was used to determine the combined effect of RA and BRL 49653 on the percentage of THP-1 cells in G1 phase (Figure 3C). In the absence of RA or BRL 49653, 34.9 ± 3.6% of cells were in G1 phase. Treatment with 1 μM BRL 49653 alone showed no change in number of cells in G1 (34.5 ± 3.5% of cells), while 10 μM BRL 49653 increased the number of cells to 41.7 ± 5.2% in G1. Treatment with 0.5, 5, or 500 nM RA progressively increased the G1 cell populations to 36.1 ± 3.9%, 40.3 ± 2.7%, and 42.7 ± 2.6%, respectively. Compared to either compound alone, the combination of RA plus BRL 49653 further increased the number of cells in G1, reaching a maximal level (53.6 ± 3.6%) at 5 nM RA plus 10 μM BRL 49653 (Figure 3C). At this combined concentration, cell proliferation is completely inhibited (Figure 3B).

To determine whether RA's effects on growth suppression were associated with effects on differentiation, the THP-1 cell surface antigens CD14 and CD15 were determined by immunocytometry analysis following treatment with 500 nM RA (Figure 4A). No difference in the cell surface expression of either of these antigens could be detected. The effects of RA on differentiation of THP-1 monocytes to macrophages were also assessed by determination of adhesion to a plastic surface, characteristic of differentiation induced by phorbal esters. To determine cell adhesion, the number of remaining suspended cells was measured after 1 day in culture (Figure 4B). No difference in the number of suspended cells was observed after 500 nM RA treatment. PMA-induced differentiation decreased the number of suspended cells by 80%. The effect of RA plus PMA treatment on cells adhesion was similar to that of PMA alone. Overall, these two control experiments show that RA-induced growth arrest does not induce differentiation.

To determine if nuclear hormone receptor induction by RA is specific to undifferentiated cells (e.g., the THP-1 monocytes, Figure 2A), we compared PPARγ1 levels to that of a differentiated THP-1 derived macrophages. In the undifferentiated THP-1 cells, PPARγ1 was induced by RA (Figure 5A), as previously shown (Figure2A). In PMA differentiated THP-1 cells, significant

levels of PPARγ1 were observed, although cells were not treated with RA. RA addition during induction of differentiation did not further increase the basal level of PPARγ1. PPARγ1 levels were also not changed in cells treated with RA following PMA induced differentiation (Figure 5B). These data indicate that undifferentiated cells are sensitive to PPARγ1 induction by RA, while differentiated cells of the same lineage are not.

DISCUSSION

The foregoing experiments establish that the induction of PPARγ1 plays an important role in RA mediated growth suppression. RA treatment suppressed cell growth and enriched the G1 cell population. In that RA is a ligand of RXR, which can heterodimerize with other nuclear hormone receptor partners (e.g., PPARα, PPARβ, PPARγ), the data indicate a potential effect of the ligand might be to induce regulation of these partners.

In the undifferentiated monocyte, PPARγ1 is expressed at low levels; however, when RA is present, the receptor RNA and protein are markedly induced (Figure 2). The PPARγ1 induction was RA concentration dependent and inversely related to cell growth suppression. At high levels of RA, growth suppression was complete; however, at low concentration of RA, cell growth was only partially impeded unless exogenous ligand (BRL 49653) to PPARγ1 was included in the growth media. These data establish that appropriate ligation of RXR/PPARγ1 may be an efficient means to completely block the proliferation of undifferentiated tumor cells. Cell cycle analysis confirmed treatment with both ligands significantly increased the proportion of cells in G1 phase when cell growth was arrested.

It should be noted that the treatments with high levels of RA or the combination of a low concentration of RA plus a PPARγ ligand blocked proliferation without inducing differentiation to macrophages. These findings contrast those in which PPARγ overexpression cause fibroblast differentiation into adipocytes. Human liposarcoma cells naturally express RXR and high levels of

PPARγ can be forced into terminal differentiation when treated with pioglitazone alone. Unlike the liposarcoma cell studies where PPARγ is highly expressed, the monocytic tumor cells used in the current study express minute amounts of PPARγ, and RA can be utilized to induce expression. It should also be noted that the combination therapy (RXR ligand plus a glitazone) caused the differentiation of the liposarcoma, as reported by Tontonoz et al., *Proc. Natl Acad. Sci. USA* 1997;94:237-241, while in the foregoing study, treatment blocked monocyte proliferation without induction of differentiation.

Growth suppression in tumor cells induced by the activation of PPARγ thus provides new therapeutic targets on human diseases associated with uncontrolled cell growth. It has been shown that the PPARγ ligand can cause growth suppression in the tumor cells with PPARγ highly expressed. The effects of PPARγ ligands on quelling tumor growth may be dependent upon the endogenous level of PPARγ expression. Indeed, if abundantly expressed, monotherapy with PPARγ ligand alone may be sufficient to block further tumor growth by induction of differentiation. However, tumors not expressing PPARγ may be resilient to PPARγ ligand monotherapy unless the receptor is induced. In the THP-1 cell model used above, proliferation was blocked without differentiation; however, other tumor types deficient in PPARγ, when subject to this dual therapeutic approach, may instead force growth suppression by differentiation. Although not tested in the current study, induction of PPARγ may have application in other forms of cellular proliferation. Perhaps, induction of PPARγ plus glitazone therapy prior to and following angioplasty, vessel transplant, or endarectomy will reduce the proliferative responses induced as a consequence of these procedures. The combinations of this invention can thus be used in these cell proliferation diseases.

The above data establish a new interaction between the retinoic acid signaling pathway an the PPAR pathway. This new interaction may have provided new therapeutic targets on the human diseases which are associated with uncontrolled cell growth. As for PPARγ function in macrophage differentiation, the data demonstrated PPARγ is upregulated during PMA treatment (induced

differentiation) in the absence of RA. Therefore, the induction of PPARγ itself in the monocyte is not sufficient to cause differentiation. Since PPARγ was also upregulated upon the PMA-induced macrophage differentiation, it shows that PPARγ plays an important role in the regulation of the macrophage function, especially with respect to uptake of lipoproteins.

CLAIMS

What is claimed is:

1. A composition comprising a retinoid and a glitazone.

2. A composition according to Claim 1 comprising 9-cis-retinoic acid.

3. A composition according to Claim 1 comprising a glitazone selected from pioglitazone, troglitazone, or rosiglitazone.

4. A composition comprising a retinoid and troglitazone.

5. A composition comprising a retinoid and pioglitazone.

6. A composition comprising a retinoid and rosiglitazone.

7. A method for inhibiting cell proliferation in a mammal comprising administering to a subject in need of treatment a cell proliferation inhibiting amount of a combination of a retinoid and a glitazone.

8. A method according to Claim 7 employing 9-cis-retinoic acid.

9. A method according to Claim 7 employing a glitazone selected from pioglitazone, troglitazone, or rosiglitazone.

10. A method for inducing the expression of PPARγ1 in mammalian cells comprising administering a PPARγ1 inducing amount of a glitazone.

11. A method according to Claim 7 employing troglitazone, pioglitazone, or rosiglitazone.

12. A method for inducing the expression of PPARγ1 in mammalian cells comprising administering a PPARγ1 inducing amount of a combination of a retinoid and a glitazone.

13. A method according to Claim 12 wherein the glitazone is selected from pioglitazone, troglitazone, and rosiglitazone.

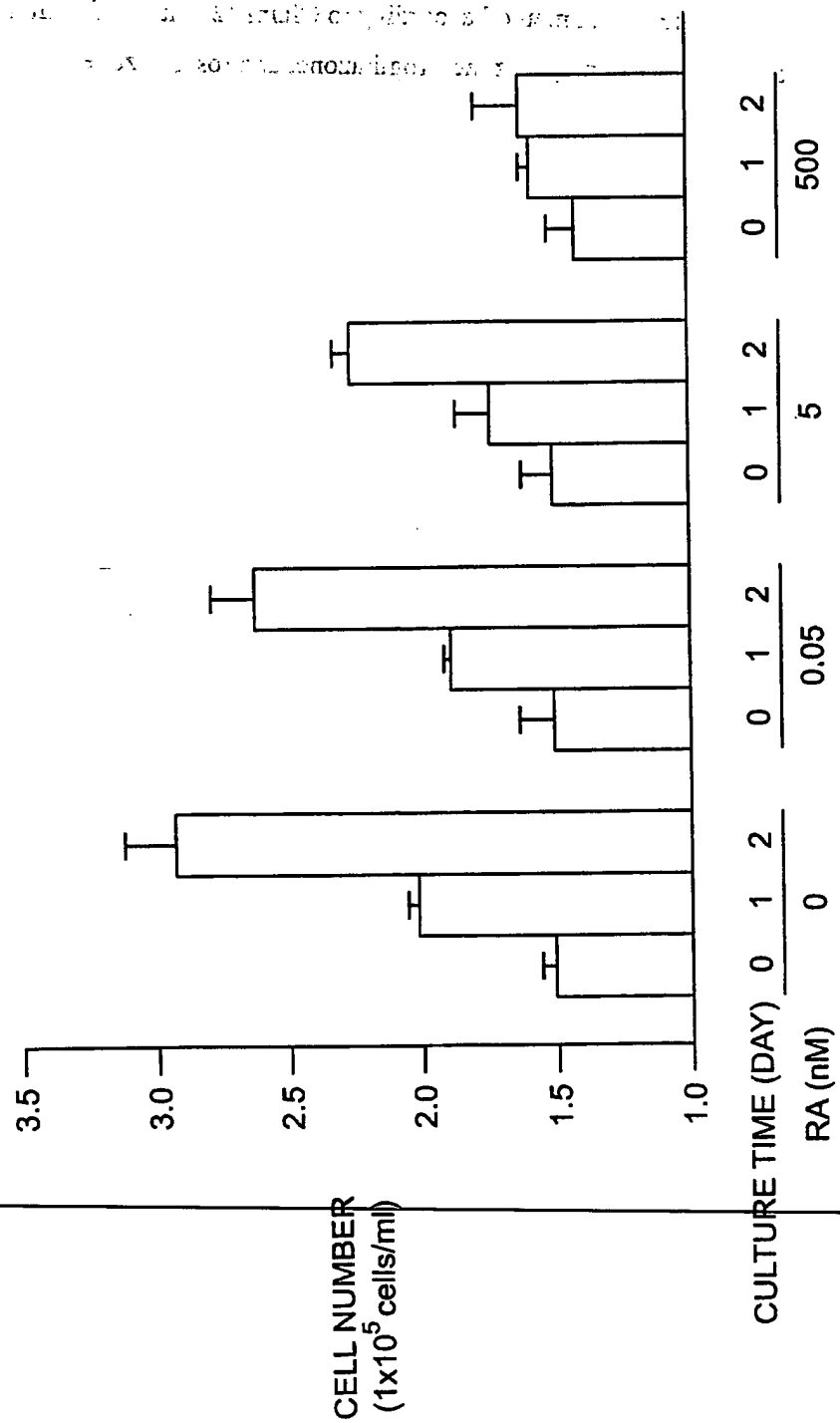
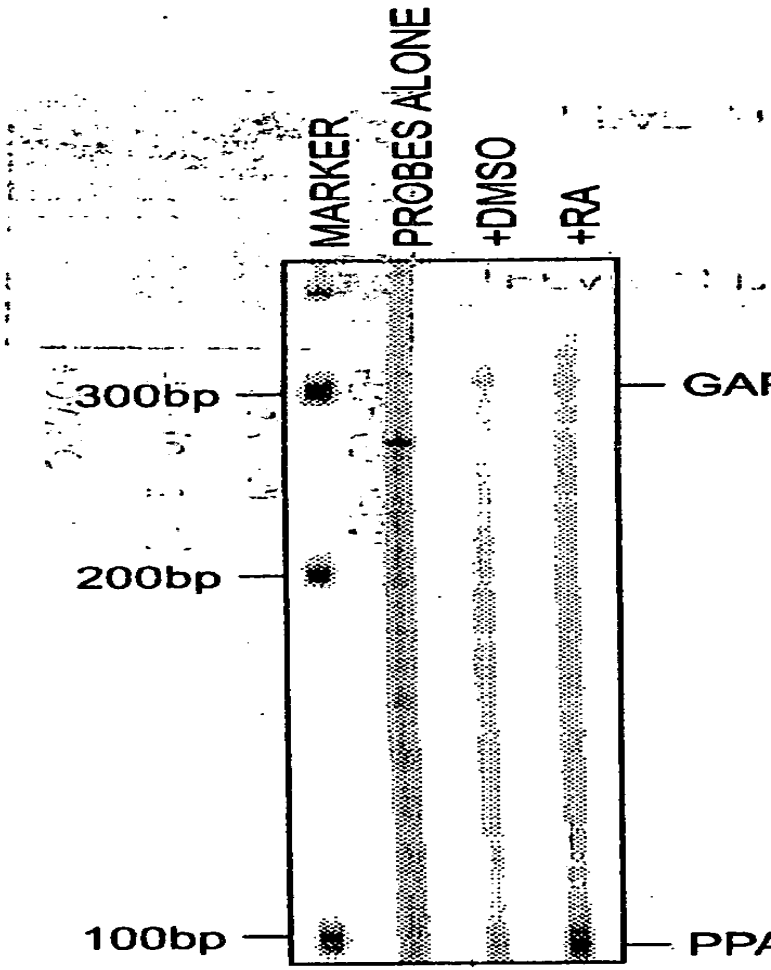

3.5
3.0
2.5
2.0
1.5
1.0
CELL NUMBER
(1x10^{5}cells/ml)
CULTURE TIME (DAY)
RA (nM)
0 1 2
0
0 1 2
0.05
0 1 2
5
0 1 2
500

FIG-1

FIG-2A



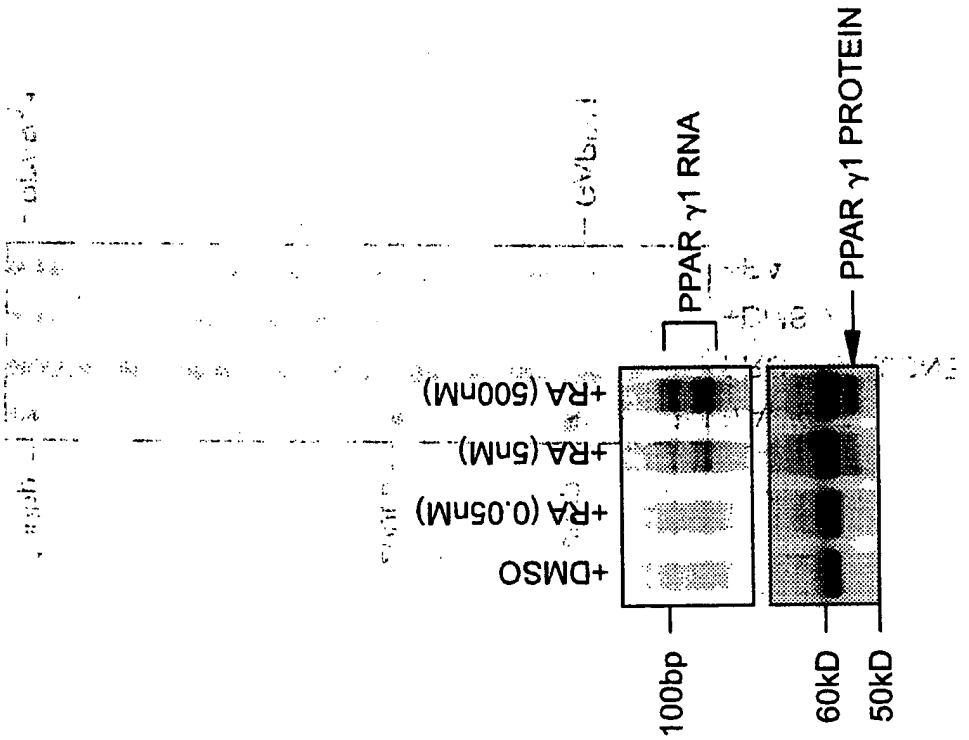
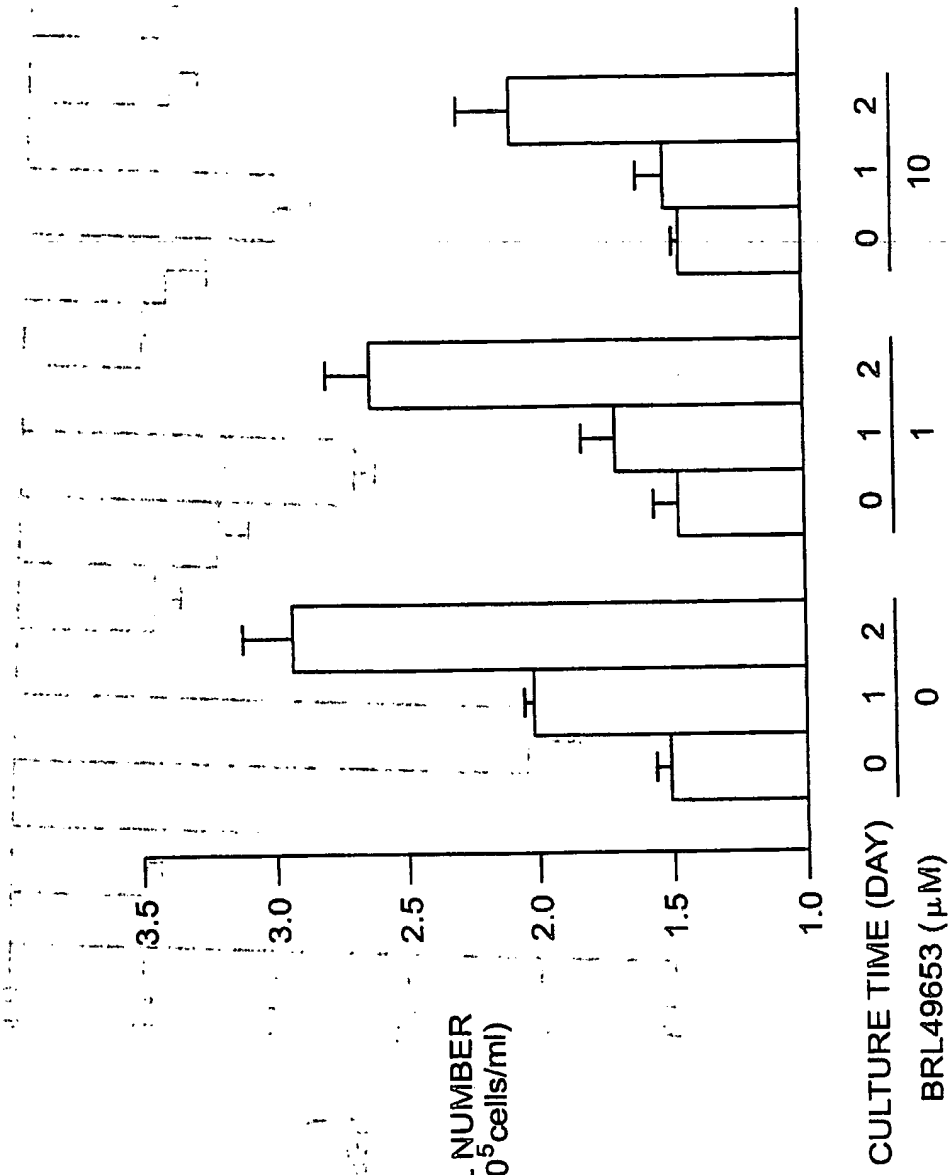

PPAR γ1 RNA
PPAR γ1 PROTEIN
+RA (500nM)
+RA (5nM)
+RA (0.05nM)
+DMSO
100bp
60kD
50kD

FIG-2B

FIG-3A


CELL NUMBER
(1x10^{5}cells/ml)
3.5
3.0
2.5
2.0
1.5
1.0
CULTURE TIME (DAY)
0 1 2
0 1 2
0 1 2
0 1 2
BRL49653 (μM)
0
1
10

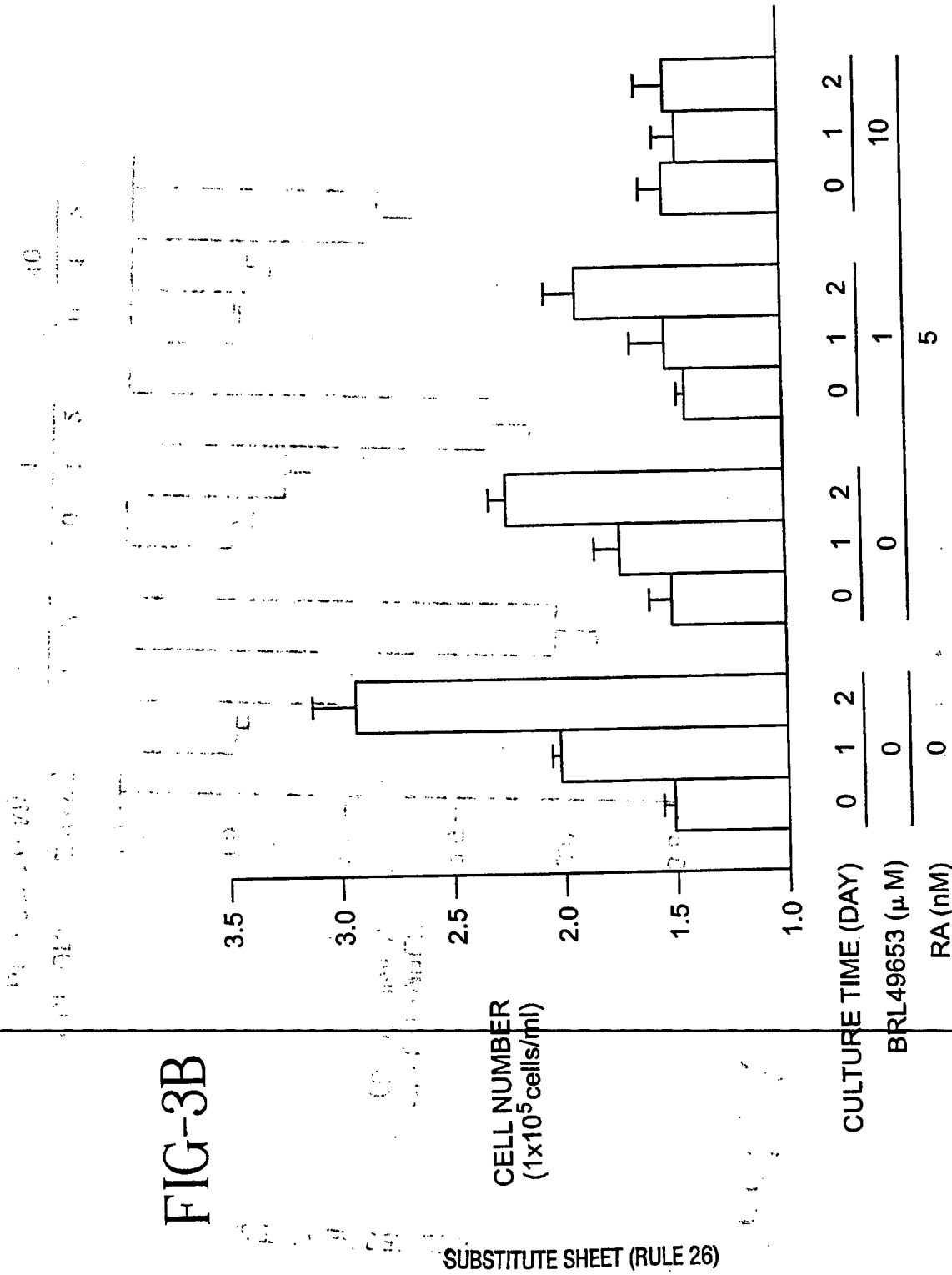
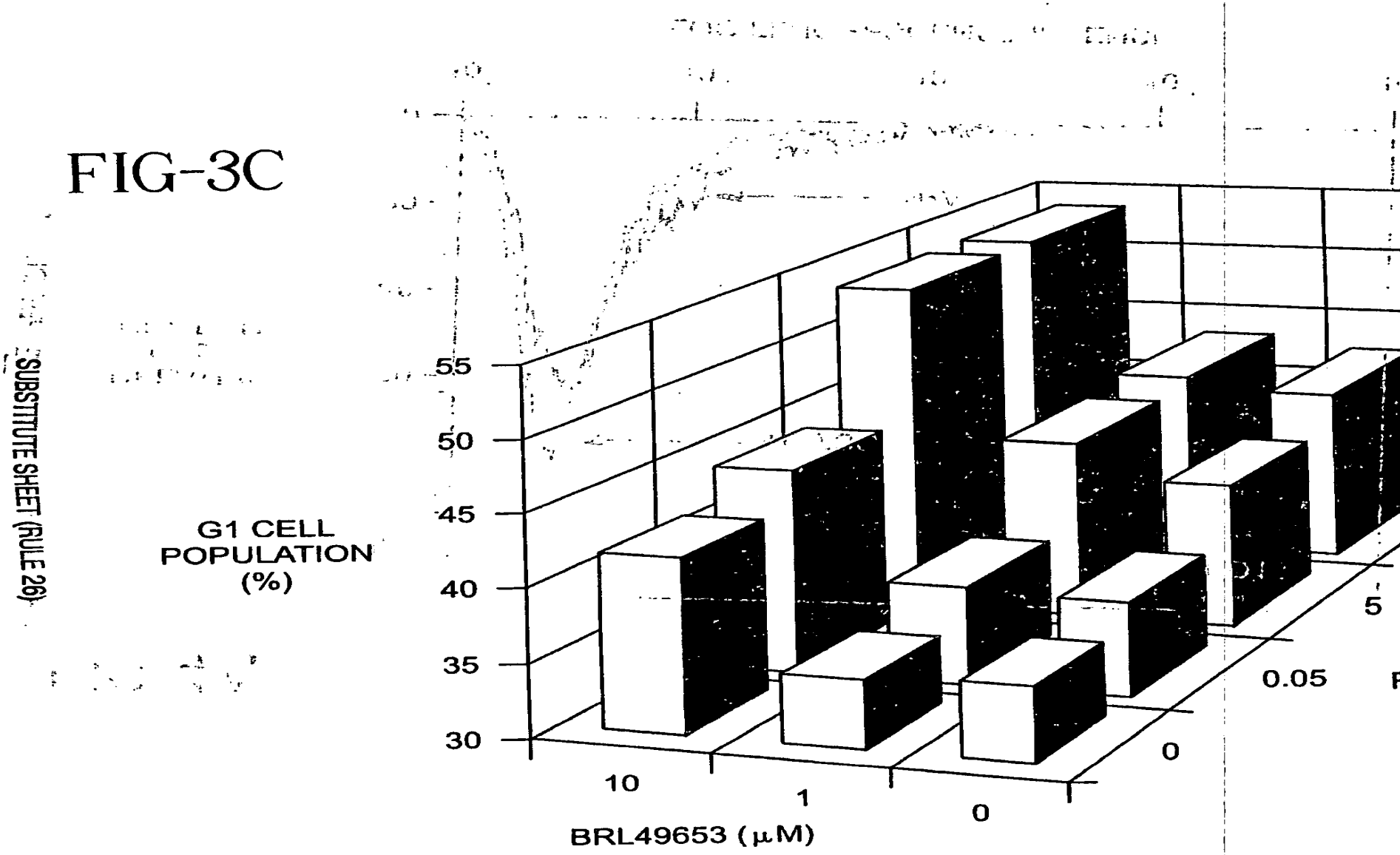

CELL NUMBER
(1x10^{5}cells/ml)
3.5
3.0
2.5
2.0
1.5
1.0
CULTURE TIME (DAY)
0 1 2 0 1 2 0 1 2 0 1 2
BRL49653 (μM)
0 0 1 10
RA (nM)
0 5

FIG-3B

FIG-3C



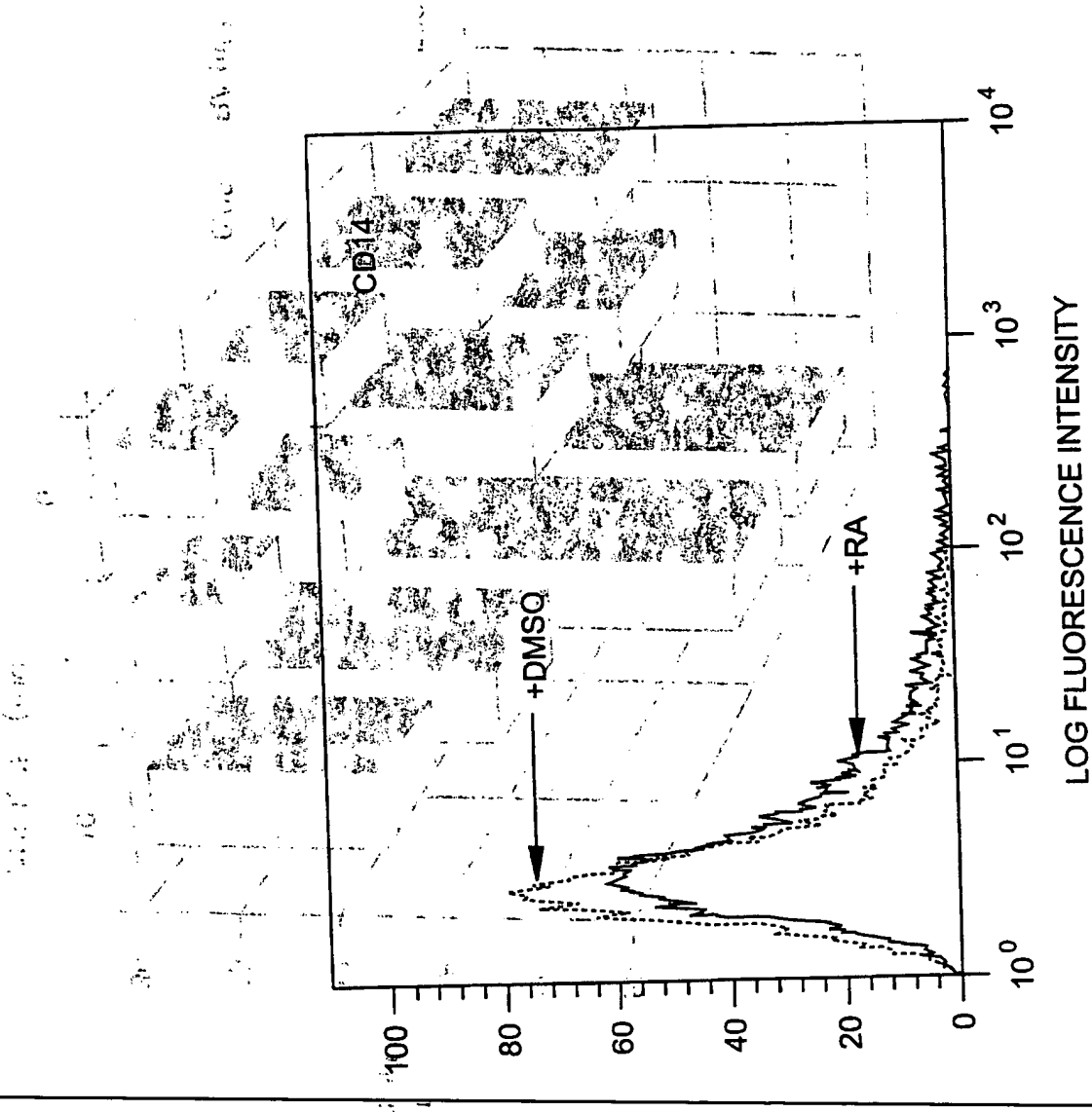

CD14
+DMSO
+RA
LOG FLUORESCENCE INTENSITY
10^0
10^1
10^2
10^3
10^4
RELATIVE CELL NUMBER
0
20
40
60
80
100

FIG-4A

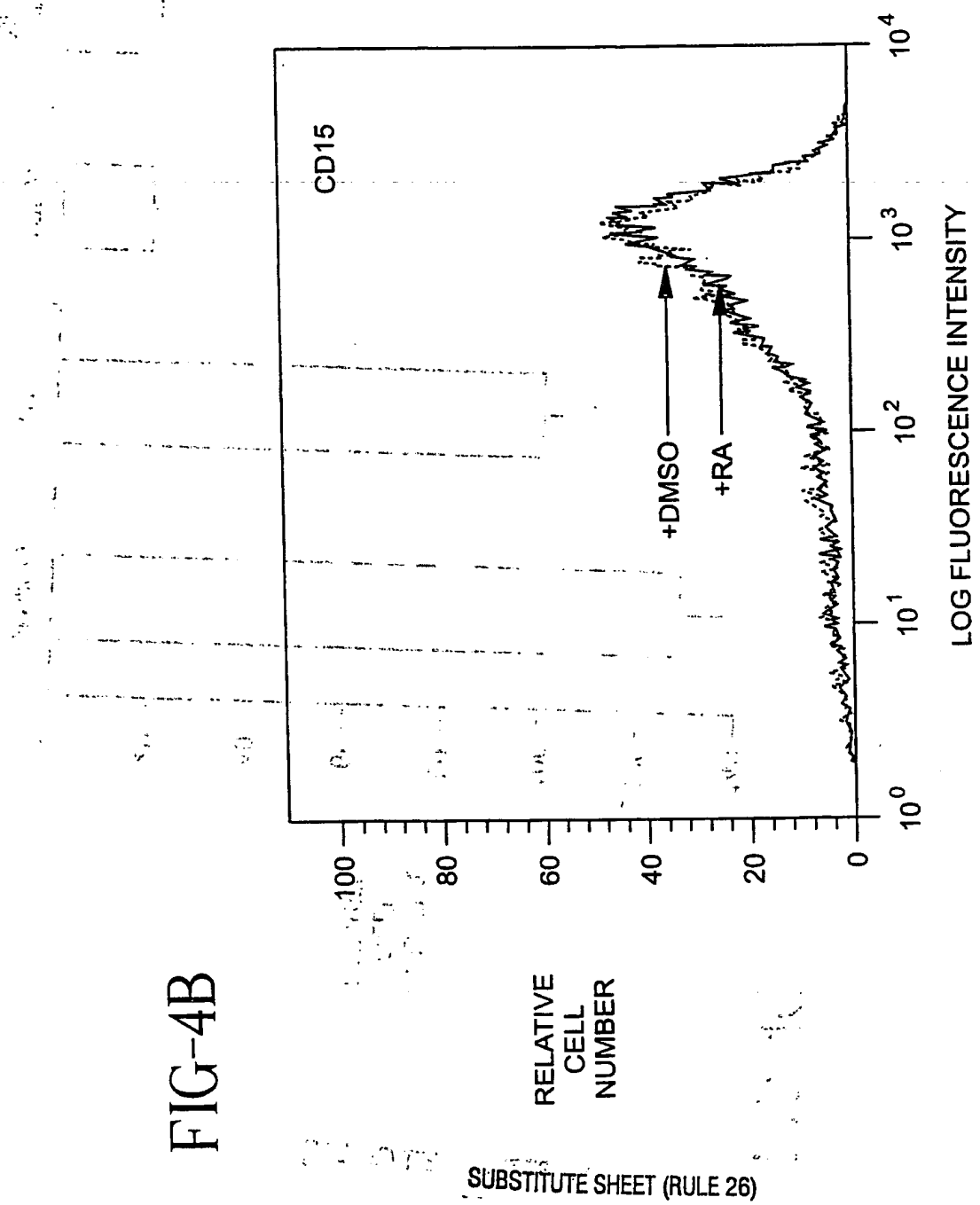

CD15
+DMSO
+RA
RELATIVE CELL NUMBER
0
20
40
60
80
100
10^0
10^1
10^2
10^3
10^4
LOG FLUORESCENCE INTENSITY

FIG-4B

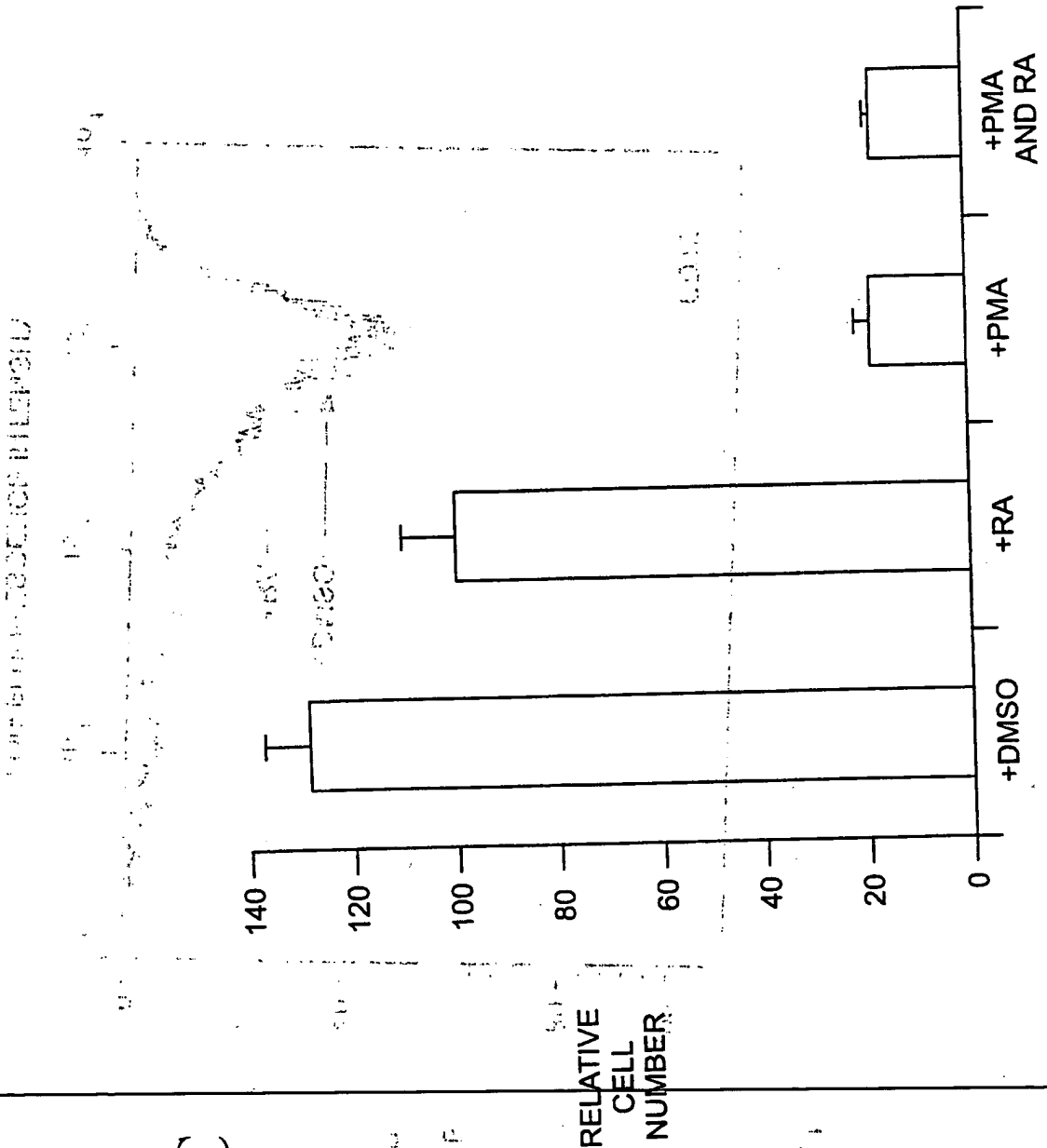

RELATIVE CELL NUMBER
0
20
40
60
80
100
120
140
+DMSO
+RA
+PMA
+PMA AND RA

FIG-4C

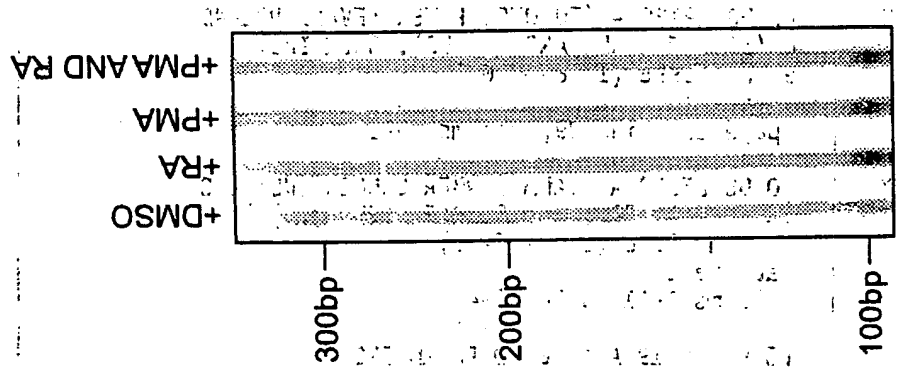


FIG-5A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25494

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/19 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 29120 A (TOTONOZ PETER ;EVANS ROLAND M (US); FORMAN BARRY M (US); SALK INST) 9 July 1998 (1998-07-09) abstract page 17, line 29; claims 1-21 ---	1-9
P,X	WO 98 25598 A (DANA FARBER CANCER INST INC ;ALTIOK SONER (US); SERRAF PASHA (US);) 18 June 1998 (1998-06-18) abstract claims 1-11,13,14,30-43 ---	1-9
X	WO 97 10819 A (LIGAND PHARM INC) 27 March 1997 (1997-03-27)	1-6
Y	claims 13-19 ---	7-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1999	07 SEP 1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tzschoppe, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/25494

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TONTONOZ P ET AL: "TERMINAL DIFFERENTIATION OF HUMAN LIPOSARCOMA CELLS INDUCED BY LIGANDS FOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AND THE RETINOID X RECEPTOR" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, January 1997 (1997-01), pages 237-241, XP002062382 cited in the application	7-9
Y	abstract page 241, left-hand column, paragraph 2 ---	1-6
Y	EP 0 552 624 A (HOFFMANN LA ROCHE) 28 July 1993 (1993-07-28) claims 1-6 ---	1-9
Y	WO 96 29069 A (ALLERGAN INC ;REGENTS BOARD OF (US)) 26 September 1996 (1996-09-26) page 2, line 18 - page 5, line 23 ---	1-9
Y	US 5 489 611 A (LEE HELEN T ET AL) 6 February 1996 (1996-02-06) column 1, line 36 - line 51; claims 1,6 ---	1-9
Y	Medline Database, abstract no. 9624260 & Am.J.Hypertens, 1996, vol. 9, no. 2, pages 188-92 XP002100863 abstract ---	1-9
Y	Medline Database, Abstract no. 97274063 & Am. J. Hypertens.; 1997, vol. 10, no. 4 Pt 1, p. 440-446 XP002100864 abstract -----	1-9

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25494

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ ~~No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is~~ restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 9

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION C NTINUED FROM PCT/ISA/ 210

1. Claims: 1-9

Compositions containing a retinoid and a glitazone and use thereof for inhibiting cell proliferation

2. Claims: 10-13

Method for inducing expression of PPARγ1 comprising administering a glitazone or a combination of a glitazone and a retinoid